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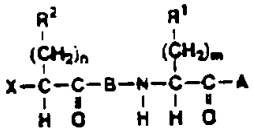
(54) [Title of the Invention] Heterocyclic Carbonyl Compounds a Thrombin Inhibiting Action

(57) [Abstract]

[Objective]

[Structure] This invention relates to compounds and pharmacologically permissible salts thereof as indicated by general formula (I) below that have inhibitory activity against thrombin and that can be used in preventing and treating thrombosis.

[Chemical Formula 18]



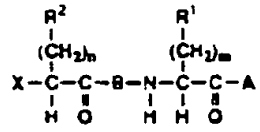
(I)

[Wherein, A indicates a heterocyclic group, R^1 indicates an alkyl group, a guanidino group, an amidino group, an amidinothio group, an amino group, an hydroxyl group, a mercapto group, a lower alkoxy group or a phenyl group that may be substituted, B indicates an amino acid residue, R^2 indicates a methyl group, a cycloalkyl group, an aryl group, a hetercaryl group or an arylthio group, X indicates a hydrogen atom, an hydroxyl group, an amino group, a halogen atom, an alkylamino group, an acylamino group or an alkoxycarbonylamino group, m indicates an integer of 1 to 50 and n indicates an integer of 0 to 4.]

[Claims]

[Claim 1] Heterocylic compounds and pharmacologically permissible salts thereof as indicated by general formula (I) below.

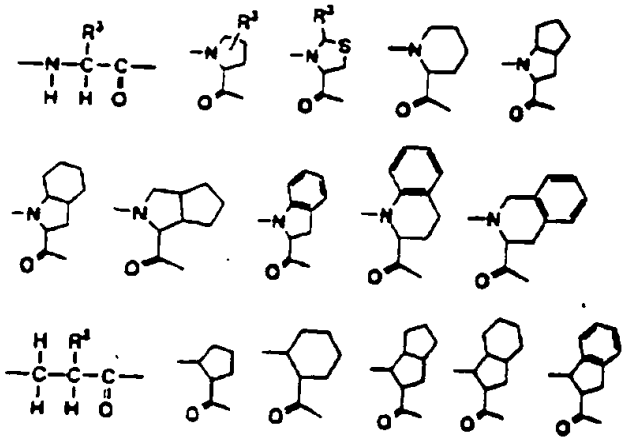
[Chemical formula 1]



(I)

[Wherein, A indicates a monoheterocyclic ring which is a 5 member or 6 member saturated, partially saturated or unsaturated ring having at least 1 nitrogen atom or diheterocyclic ring in which benzene rings or pyridine rings are condensed (which heterocyclic rings may have oxygen atoms, iodine atoms or three or less separate nitrogen atoms, in which monoheterocyclic rings, the carbon atoms in the ring, and, in which diheterocyclic rings, the carbon atoms in the benzene ring or the pyridine ring, may be substituted by lower alkyl groups having 1 to 4 carbons atoms, halogens, hydroxyl groups, amino groups or mercaptan groups, and which rings may be bonded to the carbonyl group by any of the carbon atoms that form the heterocyclic rings), R^1 indicates an alkyl group having 1 to 4 carbon atoms and which may be branched, a guanidino group, an amidinothio group, an amidino group, an amino group, an hydroxyl group, a mercapto group or a lower alkoxy group or a phenyl group that may be substituted by a guanidino group, an amidino group, an amino group, an hydroxyl group, a mercapto group or a halogen, B indicates a residue that can be selected from the following substances

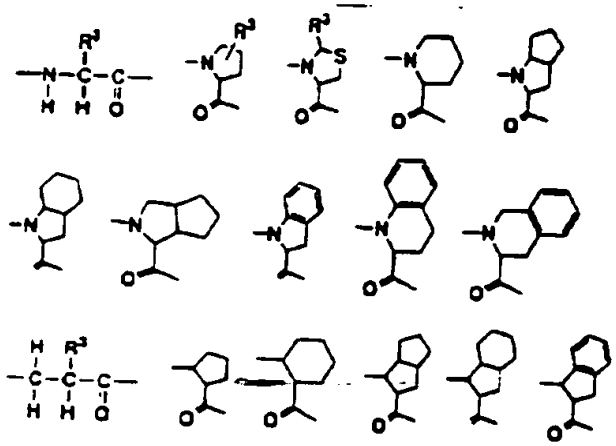
[Chemical Formula 2]



(wherein, R^1 is an alkyl group having 1 to 6 carbon atoms and which may be branched, a phenyl group or a phenylmethyl group), R^2 indicates a methyl group, an aryl group, a cycloalkyl group, a heteroaryl group, a arylthio group or a methyl group that is bonded with X, X indicates a hydrogen atom, an hydroxyl group, an amino group, a halogen atom, an alkylamino group having 1 to 4 carbon atoms, an acylamino group, an alkoxycarbonylamino group or an aryloxycarbonylamino group, m indicates an integer of 1 to 5 and n indicates an integer of 0 to 4).

[Claim 2] A heterocyclic carbonyl compound in which, in general formula (I) in Claim 1, A indicates a thiazole, an oxazole, an imidazole, a thiazoline, an oxazoline, an imidazoline, a pyridine, a pyrimidine, a pyrazole, a 1,2,4-thiadiazole, a 1,2,4-oxadiazole, a 1,2,4-triazole (which heterocyclic rings are bonded to the carbonyl group by any of the carbon atoms of which they are formed), a benzothiazole, a benzooxazole, a benzoimidazole, a thiazolo[5,4-b]pyridine, a thiazolo[4,5-b]pyridine or an imidazo[4,5-b]pyridine (which heterocyclic rings are bonded to the carbonyl group by the carbon atom in the 2nd position), R^3 indicates a guanidino group, an amidinothio group, an amidino group, an amidino group, an amino group, an hydroxyl group, a mercapto group or a lower alkoxy group or a phenyl group that may be substituted by a guanidino group, an amidino group, an amino group, an hydroxyl group, a mercapto group or halogens, B indicates a residue that is selected from substances of the following formulas

[Chemical Formula 3]



wherein R^1 has the same significances as defined in general formula (I), B indicates a methyl group, a phenyl group that may have substituted groups, a thienyl group, a pyridyl group, an indolyl group, a naphthyl group, a diphenylmethyl group, a cyclopentyl group, a cyclohexyl group, a phenylthio group or methylene that is bonded with X, X indicates a hydrogen atom, an hydroxyl group, an amino group, a halogen atom, an alkylamino group with 1 to 4 carbon atoms, an acylamino group, an alkoxycarbonylamino group or an aryloxycarbonylamino group, m indicates an integer of 1 to 5 and n indicates an integer of 0 to 4.

[Claim 3] A thrombin inhibitor that contains the heterocyclic compounds described in Claims 1 or 2 or pharmacologically permissible salts thereof as its effective components.

[0001]

[Field of industrial use] This invention relates to novel heterocyclic carbonyl compounds that have thrombin inhibiting action.

[0002]

[Prior art] Known compounds that exhibit thrombin inhibiting activity are described, for example, in Japanese Patent Application Early Disclosure No. 54-100342 [1979] and U.S. Patents No. 4399065 and 4927809. However, these existing compounds do not have sufficient thrombin inhibiting activity. Therefore, there is a demand for compounds having higher activity and enzyme selectivity.

[Synopsis of the invention]

[0003]

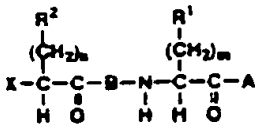
[Problems the invention is intended to solve] On the basis of research on protease inhibitors, the inventors discovered a group of novel compounds that have thrombin inhibiting activity. Consequently, this invention has the objective of providing novel heterocyclic carbonyl compounds having thrombin inhibiting activity. This invention has the further objective of providing thrombin inhibitors that contain these novel heterocyclic carbonyl compounds having thrombin inhibiting action as their effective components.

[0004]

[Means for solving the problems] The heterocyclic carbonyl compounds of this invention are the compounds indicated by general formula I below and pharmacologically permissible salts thereof.

[0005]

[Chemical Formula 4]

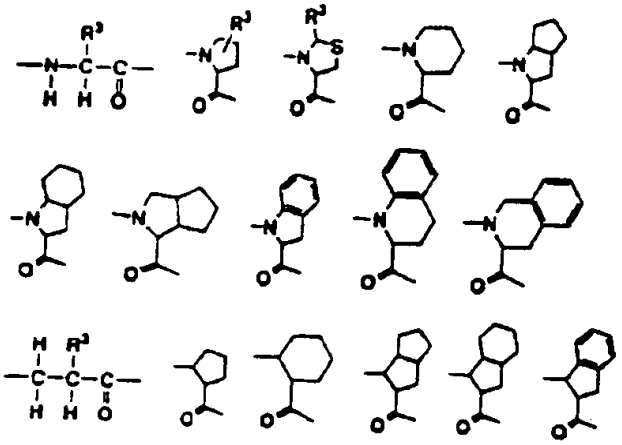


(I)

[Wherein, A indicates a monoheterocyclic ring which is a 5 member or 6 member saturated, partially saturated or unsaturated ring having at least 1 nitrogen atom or diheterocyclic ring in which benzene rings or pyridine rings are condensed (which heterocyclic rings may have oxygen atoms, sulfur atoms or three or less separate nitrogen atoms, in which monoheterocyclic rings, the carbon atoms in the ring, and, in which diheterocyclic rings, the carbon atoms in the benzene ring or the pyridine ring, may be substituted by lower alkyl groups having 1 to 4 carbons atoms, halogens, hydroxyl groups, amino groups or mercaptan groups, and which rings may be bonded to the carbonyl group by any

of the carbon atoms that form the heterocyclic rings), R^1 indicates an alkyl group having 1 to 4 carbon atoms and which may be branched, a guanidino group, an amidinothio group, an amidino group, an amino group, an hydroxyl group, a mercapto group or a lower alkoxy group or a phenyl group that may be substituted by a guanidino group, an amidino group, an amino group, an hydroxyl group, a mercapto group or a halogen, B indicates a residue that can be selected from the following substances

[Chemical Formula 5]



[wherein R^1 has the same significances as defined in general formula (I)), R indicates a methyl group, a phenyl group that may have substituted groups, a thienyl group, a pyridyl group, an indolyl group, a naphthyl group, a diphenylmethyl group, a cyclopentyl group, a cyclohexyl group, a phenylthio group or methylene that is bonded with X, X indicates a hydrogen atom, an hydroxyl group, an amino group, a halogen atom, an alkylamino group with 1 to 4 carbon atoms, an acylamino group, an alkoxycarbonylamino group or an aryloxycarbonylamino group, m indicates an integer of 1 to 5 and n indicates an integer of 0 to 4.

Further, the thrombin inhibitor and anticoagulant of this invention are substances that contain the compounds of the aforementioned general formula (I) and pharmacologically permissible salts thereof. The compounds of the aforementioned general formula (I) of this invention have strong thrombin inhibiting activity and are useful as medicinal drugs.

[0007] [Specific description of the invention] The substituted group indicated by A in general formula (I) is a monoheterocyclic ring which is a 5 member or 6 member saturated, partially saturated or unsaturated ring having at least 1 nitrogen atom or diheterocyclic ring in which benzene rings or pyridine rings are condensed (which heterocyclic rings may have oxygen atoms, sodine atoms or three or less separate nitrogen atoms, in which monoheterocyclic rings, the carbon atoms in the ring, and, in which diheterocylcic rings, the carbon atoms in the benzene ring or the pyridine ring, may be substituted by lower alkyl groups having 1 to 4 carbons atoms, halogens, hydroxyl groups, amino groups or mercaptan groups, and which rings may be bonded to the carbonyl group by any of the carbon atoms that form the heterocyclic rings). Preferably, they are monoheterocyclic rings such as a thiazole, an oxazole, an imidazole, a thiazoline, an oxazoline, an imidazoline, a pyridine, a pyrimidine, a pyrazole, a 1,2,4-thiadiazole, a 1,2,4-oxadiazole or a 1,2,4-triazole ring (which heterocyclic rings are bonded to the carbonyl group by any of the carbon atoms of which they are formed) or a diheterocylcic ring such as a benzothiazole, a benzooxazole, a benzoimidazole, a thiazolo[5,4-b]pyridine, a thiazolo[4,5-b]pyridine or an imidazo[4,5-b]pyridine ring (which heterocyclic rings are bonded to the carbonyl group by the carbon atom in the 2nd position).

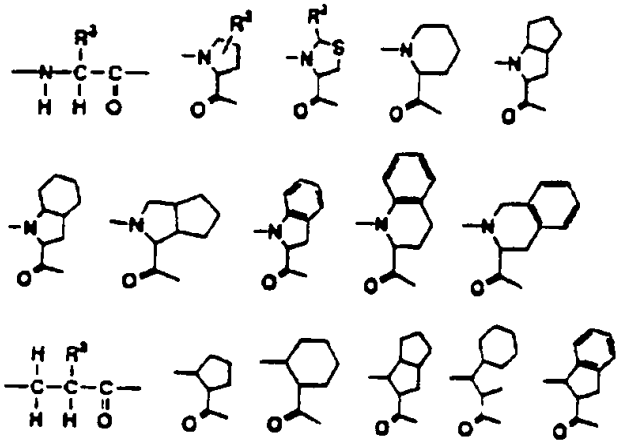
[0008] In addition, the substituted group indicated by R1 in general formula (I) is a methyl group, an isopropyl group, a guanidino group, an amidinothio group, an amidino group, an amino group, an hydroxyl group, a mercapto group, a lower alkoxy group or a phenyl group that may be substituted by a guadinino [sic] group, an amidino group, an amino group, an hydroxyl group, a mercapto group or a halogen atom and m is an integer of 1 to 5.

Preferably, R1 is a guanidino group, an amidino group or an amino group or a phenyl group that is substituted by a guanidino group, an amidino group or an amino group and m is an integer of 3 to 5.

[0009] The residues indicated by B in general formula (I) are α-amino acids, amino acid residues or straight chain or cyclic carbonyl compounds. Preferably, they are residues selected from compounds of the following structural formulas.

[0010]

[Chemical Formula 6]



(Wherein, R^3 has the same significances as defined in general formula (I).)

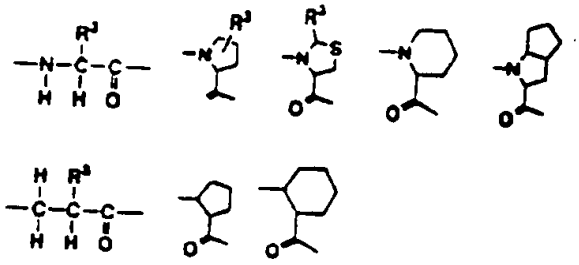
[0011] The substituted group indicated by R^2 in general formula (I) is an alkyl group that may be branched, an aryl group, a phenyl group that may be substituted, a cycloalkyl group, a heterocyclic saturated (aromatic) ring that contains 1 or 2 nitrogen atoms or a 5- or 6-member heterocyclic saturated (aromatic) ring that contains one oxygen atom or sulfur atoms, in which methylene is bonded with A and in which n is an integer of 0 to 5. Preferably, R^2 is a phenyl group, a diphenylmethyl group, a biphenyl group, a naphthyl group, a pyridyl group, a pyrrole group, an indolyl group, a thienyl group, a furanyl group or a phenylthio group and the heterocyclic ring that is formed by the methylene that is bonded with X is pyrrolidine or piperidine and n is an integer of 0 to 2.

[0012] The substituted groups indicated by X in general formula (I) are hydrogen, halogens, hydroxyl groups, amino groups, alkylamino groups, acylamino groups and alkoxycarbonylamino groups. Preferably, they are amino groups, methylamino groups, acetylamino groups, phenylacetylamino groups benzyloxycarbonylamino groups and t-butoxycarbonylamino groups.

[0013] The desirable compound groups of this invention are compounds in which, in general formula (I), A is a thiazole, R^1 is a guanidino group, B is a residue selected from substances of the following structural formulas

[0014]

[Chemical Formula 7]

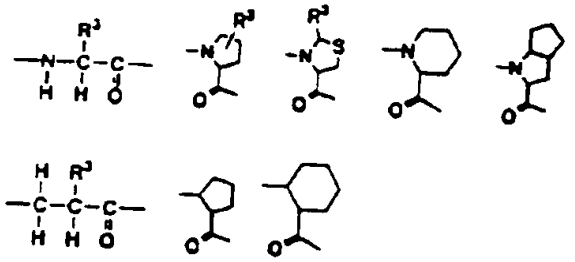


(wherein R^1 has the same significance as defined for general formula (I)), R is an aryl group, a cycloalkyl group or a phenylthio group, X is hydrogen, an amino group or a benzyloxycarbonylamino group, m is 3 and n is 0 or 1 and compounds in which A is a thiazole, R^1 is an amino group, B is a residue selected from substances of the following structural formulas

[0015]

7

[Chemical Formula 8]



(wherein R^1 has the same significance as defined for general formula (I)), R is an aryl group, a cycloalkyl group or a phenylthio group, X is hydrogen, an amino group or a benzyloxycarbonylamino group, m is 4 or 5 and n is 0 or 1.

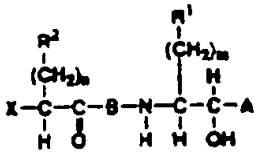
[0016] Desirable specific compounds of this invention include, for example,
D-phenylalanyl-N-[1-[2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-pyrroline amide,
D-cyclohexylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-pyrroline amide,
D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-octahydroindole-2-carboxyamide,
D-phenylglycyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide,
(benzyloxycarbonyl)-D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide,
acetyl-D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide,
phenylpropionyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide, 2-[N-[2-(phenylthioacetyl)cyclopenta-1-ylcarbonyl]-L-alginyl]thiazole,
D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-5-aminopentyl]-L-proline amide and
D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-6-aminohexyl]-L-proline amide.

[0017] Stereoisomers attributable to the carbon atoms in the molecule can be present in the compounds of this invention. All stereoisomers are included in this invention. The compounds of this invention can be salts. These salts are salts that are pharmacologically permissible. Preferably, they can be salts of hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid, acetic acid, citric acid, maleic acid, succinic acid, lactic acid, tartaric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid.

[0018] The compounds of general formula (I) can be synthesized by various methods. For example, compounds of general formula (IV)

[0021]*

[Chemical Formula 11]

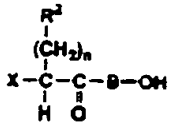


(IV)

(wherein, R^1, R^2, A, B, X, m and n have the same significances as defined previously) can be obtained by reacting compounds as indicated by general formula (II) below

[0019]

[Chemical Formula 9]

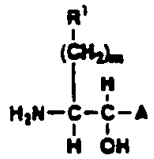


(II)

(wherein, R^2, X, B and n have the same significances as defined in general formula (I) and X indicates a group having a protective group) and compounds as indicated by general formula (III) below

[0020]

[Chemical Formula 10]



(wherein, R^1, A and m have the same significances as defined in general formula (I) and R^1 indicates a group having a protective group) with a suitable coupling reagent. When protective groups are necessary for R^1 and X in the synthesis, protective groups that are used in peptide chemistry can generally be used. Preferably, they can be t-butoxycarbonyl groups, benzyloxycarbonyl groups and 4-methoxy-2,3,6-trimethylbenzenesulfonyl groups.

[0022] Reagents that are used in peptide chemistry can be used as the coupling reagents. Desirable coupling reagents include, for example, N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, N,N'-bis[2-oxo-3-oxazolidinyl]phosphonediamide acid chloride and diphenylphosphinyl chloride. In the presence of these reagents, the reaction can be performed in a suitable solvent (for example, ethyl acetate, acetonitrile, methylene chloride, DMF) at -70 to 30°C, and, preferably, -10 to 10°C.

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*Translator's note: To provide proper English syntax, the sections have been rearranged from the Japanese.

[0023] Next, the hydroxyl group of compound (IV) is oxidized to form a ketone. As required, the protective group can be removed and the heterocyclic carbonyl compound of general formula (I) can be obtained. The oxidation reaction can be performed with dimethyl sulfoxide using various types of additives as described in Synthesis, 1990, page 857. Oxidation can also be performed by means of tetra-n-propylammonium perthenate [phonetic]**, pyridinium dichromate and pyridinium chlorochromate. Oxidation by means of dimethyl sulfoxide in the presence of oxalyl chloride is preferable. For example, the compounds of general formula (I) can be obtained by reacting a reagent prepared from oxalyl chloride and dimethyl sulfoxide with compound (IV) at -70 to 0°C using methylene chloride as the solvent, after which treatment is performed with triethylamine.

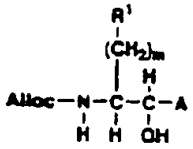
[0024] Moderate reaction conditions can be selected to obtain compounds of general formula (I) when a reaction to eliminate protection is required. For example, when the protective groups described above are used, the protection can be eliminated by hydrocracking using palladium-carbon as the catalyst or by an acid decomposition reaction in which trifluoroacetic acid is reacted in the presence of anisole and thioanisole.

[0025] The compounds of general formula (I) of this invention form acid addition salts with various inorganic acids and organic acids. Compound (I) that is obtained by the aforementioned reactions can be isolated in free form or in the form of a salt. When it is in free form, the acid addition salt can be obtained by reaction with the desired acid.

[0026]* In order to obtain the aforementioned amine compound (III), which is the starting substance, the carbinol compound (VII)

[0029]

[Chemical Formula 14]

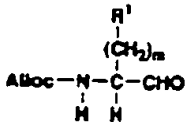


(VII)

can be obtained by reacting the aminocarbinol compound (V), which is obtained by the method described in Chemical Review, 1989, Vol. 89, page 149.

[0027]

[Chemical Formula 12]



(V)

wherein R¹ and m have the same significances as defined in general formula (II) and Alloc indicates allyloxycarbonyl group) with the silyl compound (VIa) described in Journal of Heterocyclic Chemistry, 1971, Vol. 8, page 257 and Journal of Organic Chemistry, 1988, Vol. 53, page 1748.

**Translator's note: Transliterated phonetically from the Japanese. As such, the spelling may differ from other transliterations.

[0028]

[Chemical Formula 13]

$(CH_3)_3Si\text{-}A$ (VIa)

(wherein A has the same significances as defined in general formula (I)). Preferably, this reaction can be performed using methylene chloride as the solvent at 0 to 50°C in the presence or absence of cerium fluoride and tetrabutylammonium fluoride. Compound (VII) can also be obtained by treating the heterocyclic compound (H-A), which is the starting substance, with a base such as n-butyl lithium in an inactive solvent (for example, tetrahydrofuran and dimethoxyethane) to form compound (VIb)

[0030]

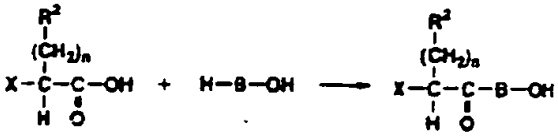
[Chemical Formula 15]

Li^+A^- (VIb)

which is then reacted with the aforementioned compound (V). The aforementioned amine compound (III) can be obtained by treating and eliminating the amino group protective group of compound (VII), for example, pyrrolidine in the presence of $Pd(Ph_3P)_4$, which is a known method. The aforementioned carboxylic acid compound (II), which is also a starting substance, can be obtained by ordinary methods of peptide chemistry when B-OH is an amino acid residue. Compound (II) can be obtained by introducing the carboxylic acid compound (VIII) into a reactive derivative (for example, an acid halide, an acid anhydride or an active ester) and by reacting it with an alkali metal salt of the amino acid (IX) or a salt of an organic base. Preferably, compound (VIII) can be reacted with N-hydroxysuccinic acid amide to convert it to an active ester which is then reacted with the amino acid (IX) in the presence of an organic base to form a peptide bond.

[0032]

[Chemical Formula 16]

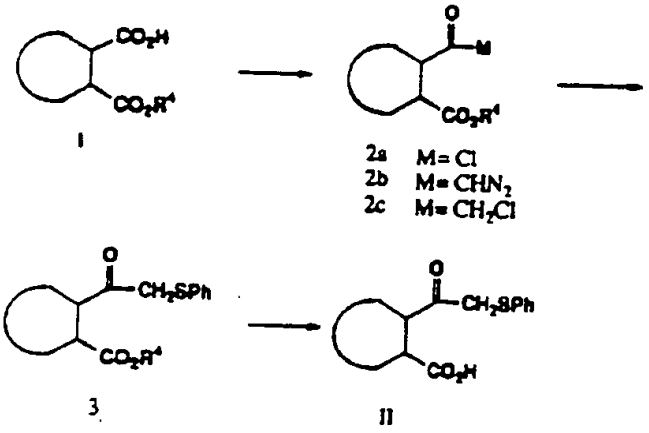


(VIII) (IX) (II)

When B-OH of the aforementioned compound (II) is an aliphatic carboxylic acid, it can be obtained from a cyclic or straight chain dicarboxylic acid. For example, with a cyclic dicarboxylic acid, the monoalkyl ester (1) is reacted with a thionyl chloride or oxalyl chloride to form an acid chloride (2a), which is then treated with diazomethane to convert it to diazomethyl ketone (2b). This ketone is reacted with anhydrous hydrogen chloride to form the chloromethyl ketone (2c), which is then converted to phenylthiomethyl ketone (3) by treating it with thiophenyl. The carboxylic acid compound (II) can be obtained by hydrolyzing the ester of this compound.

[0033]

[Chemical Formula 17]



(Wherein, R^4 indicates a methyl group, a benzyl group or a diphenylmethyl group.)

[0034] Because compound (I) of this invention and its acid addition salts exhibit a strong, selective inhibitory action against thrombin, it is useful as a diagnostic drug for determining thrombin in the blood, as a platelet coagulation inhibitor and in the prevention and treatment of thrombosis.

[0035] Thrombin inhibitors which contain compounds of this invention as indicated by general formula (I) and pharmacologically permissible salts thereof as their effective components can be used in various forms suited to oral and parenteral administration (for example, inhalation administration, nose drops, eye drops, subcutaneous administration, intravenous injection, intramuscular injection, etc.)

[0036] For example, depending on its intended use, they can be prepared as oral agents in such forms as tablets, capsules, granules, powders, fine grains, troches, syrups and emulsions, as inhalation agents, as solutions for topical use in the form of nose drops and eye drops and as injection agents for intravenous injection and intramuscular injection. These preparations can be manufactured by standard methods using vehicles, extending agents, binders, wetting agents, disintegrators, lubricants, dispersants, buffering agents, preservatives, auxiliary dissolution agents, antiseptics and stabilizers that are commonly used.

[0037] The content of the compound of this invention in a drug preparation differs depending on the form of the preparation. Ordinarily, it is 1 to 70 wt%, and, preferably, 5 to 50 wt %, of the total composition. The dose and the method of administration are determined appropriately taking into consideration the age and sex of the patient and the degree of symptoms. Ordinarily, for adults, it should be on the order of approximately 0.1 to 2000 mg, and, preferably, 5 to 400 mg, per day. It can be administered once or several times a day.

[0038] Method of determination of in vitro inhibitory activity

Thrombin inhibiting activity in an in vitro system was found by the method described in the European Journal of Biochemistry, 1988, Vol. 172, page 17. A mixed solution of 100 ml of 0.1 M trishydrochloric acid solution (pH 8.0; containing 0.3 M NaCl and 2 mM $CaCl_2$), a 10 ml DMSO solution of the compound of this invention, 50 ml of bovine serum albumin solution (0.4 mg/ml) and 20 ml of thrombin (0.5 U/ml) dissolved in the aforementioned trishydrochloric

acid solution was prepared. To this was added 20 ml of 3 mM Boc-Asp(OBzl)-Pro-Arg-methylcoumarin amide solution (10% DMSO), which was the substrate and the mixture was incubated for 30 minutes at 37°C, after which fluorescence intensity (a1) of 440 nm excited by 380 nm UV was determined. At the same time, an experiment was performed in which DMSO was used instead of the solution of the compound of this invention and fluorescence intensity (a2) was determined in the same way. In addition, the fluorescence intensity (b) of a mixed solution of 120 ml of the aforementioned 0.1 M trishydrochloric acid buffer solution, 10 ml of DMSO solution, 50 ml of bovine serum albumin solution and 20 ml of substrate solution was determined as background. Inhibition rates were calculated by the following formula and the concentration required for 50% inhibition (IC_{50}) was found.

$$\text{Inhibition rate (\%)} = [[(a2-b) - (a1-b)] / (a2-b)] \times 100$$

The experimental results for representative compounds of this invention are shown in Table 1.

Table 1. Thrombin Inhibition Activity

Example No. of compound	50% inhibition concentration
1	0.0018
2	0.16
4	0.012
5	0.32
7	0.007
8	0.002
Argatroban*	0.065

* Compound described in Japanese Patent Disclosure No. 61-46829 (1986)

[0039]

[Examples] We shall now describe the compounds of this invention in detail by presenting examples as indicated below. However, they are simply illustrations and do not limit this invention in any way.

[0040] Example 1

D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

(a)
t-butoxycarbonyl-D-phenylalanyl-N-[1-[(2-thiazolyl)hydroxymethyl]-4-[N',N"-bis(t-butoxycarbonyl)aminoiminomethyl]amino]butyl]-L-proline amide

t-butoxycarbonyl-D-phenylalamyl-L-proline (300 mg, 0.82 mmol), 2-[2-amino-5-[N',N"-bis(t-butoxycarbonyl)aminoiminomethyl]amino-1-hydroxypentyl]thiazole (367 mg, 0.82 mmol) and N-hydroxbenzotriazole (110 mg, 0.82 mmol) were dissolved in 15 ml of acetonitrile and 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride (187 mg, 0.98 mmol) was added as the materials were being ice-cooled. The mixture was stirred at the same temperature for 3 hours. The temperature was then raised to room temperature and it was stirred for 15 hours. The reaction mixture was concentrated, after which it was dissolved in ethyl acetate, washed with water and dried in $MgSO_4$. The solvent was removed, the crude product was purified by flash chromatography and the target compound (497 mg, 77%) was obtained.

^{1}H-NMR($CDCl_3$) δ 1.42-1.62 (m, 32H), 1.79-1.89 (m, 2H), 2.47-2.80 (m, 1H), 1.93-3.00 (m, 2H), 3.33-3.43 (m, 4H), 4.01-4.04 (m, 1H), 4.06-4.09 (m, 1H), 4.43-4.60 (m, 1H), 4.98-5.02 (m, 1H), 5.47-5.50 (m, 1H), 7.18-7.29 (m, 6H), 7.71-7.75 (m, 1H), 8.33-8.36 (m, 1H).

[0041] (b)
D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-proline amide

Oxazolyl chloride (79 ml, 0.91 mmol) was dissolved in 8 ml of methylene chloride, dimethyl sulfoxide (129 ml, 0.91 mmol) was added at -40°C and the mixture was stirred for 5 minutes. 5 ml of methylene chloride solution containing the aforementioned compound (480 mg, 0.61 mmol) was added and the mixture was stirred for 30 minutes at -40 to -30°C. Next, triethylamine (581 ml, 4.1 mmol) was added and the mixture was stirred at the same temperature for 30 minutes, after which it was emptied into ice water. The organic layer was separated and washed with water, after which it was desiccated with $MgSO_4$ and concentrated. The product was refined by flash chromatography and t-butoxycarbonyl-D-phenylalanyl-N-[1-[(2-thiazolyl) carbonyl]-4-[N',N"-bis(t-butoxycarbonyl)aminoiminomethyl]amino]butyl]-L-proline amide (407 mg, 86%) was obtained. This compound was dissolved in 1 ml of anisole and 4 ml of trifluoroacetic acid was added as the materials were being ice cooled. The mixture was stirred at the same temperature for 30 minutes and was then stirred at room temperature for 30 minutes. The reaction mixture was concentrated, dissolved in 5 ml of water and washed with ether, after which it was freeze dried and the target substance (407 mg) was obtained. ^{1}H-NMR(D_2O) δ 1.59-1.60 (m, 32H), 1.70-1.91 (m, 2H), 2.12-2.14 (m, 2H), 2.75-2.81 (m, 1H), 3.15-3.29 (m, 4H), 3.50-3.54 (m, 1H), 4.43-4.46 (m, 1H), 4.53-4.61 (m, 1H), 5.49-5.55 (m, 1H), 7.32-7.46 (m, 5H), 8.11-8.15 (m, 2H), MS (SIMS) m/z (M^{+1}).

[0042] (c) Synthesis of intermediate

The 2-[2-amino-5-[N',N"-bis(t-butoxycarbonyl)aminoiminomethyl]amino-1-hydroxypentyl]thiazole that was used in this example was synthesized by the following method. L-arginine (10 g, 57 mmol) was dissolved in 60 ml of water, allyl chloroformate (8.99 mg, 74 mmol) was added under ice-cooled conditions as the pH was maintained at 9 to 10 with 4N-NaOH, the pH was adjusted to 7 and the mixture was stirred at the same temperature for 2 hours. The precipitate that separated out was collected by filtration and was washed with a small quantity of ice water and acetone. It was then desiccated and N-allyloxycarbonyl-L-arginine (13.3 g, 90%) was obtained. The aforementioned compound (10 g, 39 mmol) and p-toluenesulfonic acid (7 g, 37 mmol) was dissolved in 250 ml of methanol, diphenyldiazomethane (15 g, 78 mmol) was added over a one hour period and the mixture was stirred for 3 hours at room temperature, after which it was concentrated. The reaction product was dissolved in chloroform and washed with water, after which it was desiccated with $MgSO_4$ and concentrated, with N-allyloxycarbonyl-L-arginine diphenylmethyl ester p-toluenesulfonate (24 g) being obtained. The aforementioned crude product (24 g) was dissolved in 250 ml of acetonitrile, dimethylaminopyridine (4.7 g, 39 mmol) and bis-t-butyldicarbonate (21 g, 97 mmol) were added and the mixture was stirred for 15 hours at room temperature, after which it was concentrated. The reaction mixture was dissolved in ethyl acetate and washed in water, after which it was concentrated. It was then refined by silica gel chromatography (n-hexane/ethyl acetate) and Nα-allyloxycarbonyl-N',N"-bis(t-butoxycarbonyl)-L-arginine diphenyl methyl ester (14.5 g, 60%) was obtained.

[0043] The aforementioned compound (11 g, 18 mmol) was dissolved in 150 ml of tetrahydrofuran. $LiBH_4$ (0.75 g, 35 mmol) was added and the mixture was stirred for 2 hours at room temperature. The reaction mixture was poured into acidic water at pH 3, extraction was performed with ethyl acetate and the organic layer was washed with water, after which it was desiccated with $MgSO_4$ and concentrated. The reaction product was refined by silica gel chromatography (n-hexane/ethyl acetate) and Nα-allyloxycarbonyl-N',N"-bis(t-butoxycarbonyl)- L-arginol (3.9 g, 50%) was obtained.

^{1}H-NMR($CDCl_3$) δ 1.35-1.80 (m, 22H), 3.30-3.80 (m, 6H), 4.58 (d, J = 5.02 Hz, 1H), 5.22 (dd, J = 1.55, 10.0 Hz, 1H), 5.31 (dd, J = 1.55, 17.6 Hz, 1H), 5.49 (d, J = 7.53 Hz, 1H), 5.93 (ddd, J = 5.02, 10.0, 17.6 Hz, 1H), 8.38

(t, J = 5.02 Hz, 1H). Oxazolyl chloride (1.27 g, 10 mmol) was dissolved in 40 ml of methylene chloride, dimethyl sulfoxide (1.57 g, 20 mmol) was added at -30°C, after 5 minutes, 20 ml of methylene chloride solution containing the aforementioned carbinol compounds (3.0 g, 6.7 mmol) was added and the mixture was stirred for 30 minutes at -30°C. Next, triethylamine (4.62 g, 45 mmol) was added and the mixture was stirred for 30 minutes at -30°C, after which it was emptied into ice water and the solutions were separated. The organic layer was washed with water, after which it was desiccated with $MgSO_4$ and concentrated, with
Nα-allyloxycarhbonyl-N',N"-bis(t-butoxycarbonyl)-L-arginal (2.9 g) being obtained.

[0044] The aforementioned crude product (2.9 g) and 2-trimethylsilylthiazole (1.54 mg, 9.8 mmol) were dissolved in 50 ml of methylene chloride and the solution was stirred for 5 hours at room temperature. 1M tetra-n-butylammonium fluoride THF solution (10.4 ml) was added, the mixture was stirred for another 30 minutes and was then emptied into ice water. The organic layer was separated, desiccated with $MgSO_4$ and concentrated. It was then refined by silica gel chromatography (n-hexane/ethyl acetate) and 2-[2-allyloxycarbonylamino-5-[N',N"-bis(t-butoxycarbonyl)aminoiminomethyl]amino-1-hydroxypentyl]thiazole (2.1 g, 60%) was obtained.

^{1}H-NMR($CDCl_3$) δ 1.35-1.86 (m, 22H), 3.30-3.55 (m, 2H), 4.05-4.22 (m, 1H), 4.43-4.65 (m, 2H), 5.06-5.40 (m, 4H), 5.78-6.02 (m, 2H), 7.28 (d, J = 3.0 Hz, 1H), 7.73 (d, J = 3.0 Hz, 1H), 8.48 (t, J = 6.24 Hz, 1H).

[0045] The aforementioned compound (2.1 g) was dissolved in 35 ml of methylene chloride, piperidine (1.34 g, 19 mmol) and $Pd(Ph_3P)_4$ (220 mg, 0.19 mmol) was added and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was concentrated and refined by silica gel chromatography (chloroform/methanol), with the target compound (1.42 g, 85%) being obtained.

^{1}H-NMR($CDCl_3$) δ 1.40-1.80 (m, 22H), 3.17-3.55 (m, [sic] 4.70-4.80 (m, 1H), 4.88-4.98 (m, 1H), 7.40-7.80 (m, 3H), 8.30-8.43 (m, 1H).

[0046] Example 2

<u>2-[2-[2-(phenylthioacetyl)cyclopenta-1-ylcarbonyl]-L-arginyl]thiazole</u>

(a)
2-[2-[2-(phenylthioacetyl)cyclopenta-1-ylcarbonyl]amino-5-[N',N'-bis(t-butixycarbonyl)aminoiminomethyl]amino-1-hydroxypentyl]thiazole

2-(phenylthioacetyl)cyclopentanecarboxylic acid (249 mg, 0.94 mmol), 2-[2-amino-5-[N',N'-bis(t-butoxycarbonyl)aminoiminomethyl]amino-1-hydroxypentyl]thiazole (417 mg, 0.94 mmol) and N-hydroxybenzotriazole (126 mg, 0.94 mmol) were dissolved in 20 ml of acetonitrile, 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride (215 mg, 0.98 mmol) was added under ice-cooled conditions, the mixture was stirred at this same temperature for 3 hours, the temperature was then raised to room temperature and it was stirred for 15 hours. The reaction mixture was concentrated, after which it was dissolved in ethyl acetate. It was then washed with water, after which it was desiccated with $MgSO_4$. The solvent was removed, the crude product was refined by flash chromatography and the target compound (438 mg, 68%) was obtained.

^{1}H-NMR($CDCl_3$) δ 1.20-2.10 (m, 28H), 2.87 (m, 1H) 3.30-3.50 (m, 3H), 3.24 (m, 1H), 4.25 (m, 1H), 5.03 (m, 1H), 6.75 (m, 1H), 7.15-7.40 (m, 5H), 7.43-7.57 (m, 1H), 7.70 (m, 1H), 8.37 (m, 1H).

[0047] (b) 2-[2-(phenylthioacetyl)cyclopentane-1ylcarbonyl-L-arginyl]thiazole
oxalyl chloride (81 ml, 0.93 mmol) was dissolved in 10 ml of methylene chloride, dimethyl sulfoxide (132 ml, 1.87 mmol) was added at -40°C and the mixture was stirred for 5 minutes. [redacted] ml of methylene chloride solution containing the aforementioned compound (430 mg, 0.62 mmol) was added and the mixture was stirred for 30 minutes at -40 to -30°C. Next, triethylamine (596 ml, 4.2 mmol) was added and the mixture was stirred at this same

temperature for 30 minutes, after which it was emptied into ice water. The organic layer was separated and washed with water, after which it was desiccated with $MgSO_4$ and concentrated. The product was purified by flash chromatography and 2-[2-(phenylthioacetyl)cyclopentane-1-ylcarbonyl-N',N'-bis(t-butoxycarbonyl) arginyl]thiazole (350 mg, 83%) was obtained. This compound was dissolved in 1 ml of anisole, 4 ml of trifluoroacetic acid was added under ice-cooled conditions, the mixture was stirred at this same temperature for 30 minutes and was then stirred for 30 minutes at room temperature. The reaction mixture was concentrated and refined by flash chromatography (chloroform/methanol), with the target compound (254 mg) being obtained.

^{1}H-NMR(CD_3OD) δ 1.60-2.20 (m, 10H), 3.05 (m, 1H) 3.24 (m, 2H), 3.53 (m, 1H), 3.90 (m, 2H), 5.56 (m, 1H), 7.10-7.40 (m, 1H), 7.10-7.40 (m, 5H), 8.05 (m, 1H), 8.12 (m, 1H), MS(FD) m/z 488 (M^+).

[0048] (c) Synthesis of intermediate

The 2-phenylthiomethylcarbonylcyclopentane-1-carboxylic acid that was used in this example was synthesized by the following method. 2-[(diphenyl) methoxycarbonyl]cyclohexane-1-carboxylic acid (2.0 g, 6.17 mmol) and triethylamine (0.944 ml, 6.79 mmol) were dissolved in 20 ml of methylene chloride, N,N-dimethylformamide (1 drop) and oxalyl chloride (855 mg, 6.79 mmol) were added under ice-cooled conditions and the mixture was stirred for 1 hour. Next, an ether solution containing an excess of diazomethane was added under ice-cooled conditions and the mixture was stirred for 30 minutes. A 4N-HCl dioxane solution (2.31 ml) was then added and the mixture was stirred for another 30 minutes. The reaction product was concentrated, the chloromethyl ketone that was produced was dissolved in 30 ml of tetrahydrofuran, disiopropyl ethylamine (815 mg, 6.32 mmol) and thiophenol (690 mg, 6.32 mmol) were added and the mixture was stirred for 3 hours at room temperature, after which it was concentrated. The reaction product was refined by silica gel chromatography (toluene/acetic acid) and phenylthiomethyl ketone (2.12 g, 86%) was obtained. This product was dissolved in 200 ml of methanol, a 1M aqueous solution of potassium carbonate (9.74 ml) was added and the mixture was stirred for 15 hours at room temperature. The reaction mixture was concentrated and the residue was dissolved in water and washed with ether. The aqueous layer was acidified, after which extraction was performed with ethyl acetate. It was then desiccated with $MgSO_4$ and concentrated, with the target compound (0.97 g, 76%) being obtained.

^{1}H-NMR($CDCl_3$) δ 1.60-2.10 (m, 6H), 3.20 (m, 1H) 3.58 (m, 1H), 3.80 (s, 2H), 7.15-7.40 (m, 5H).

[0049] Example 3

<u>D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-5-aminopentyl]-L-proline amide</u>

(a) t-butoxycarbonyl-D-phenylalanyl-N-[1-[2-thiazolyl)hyxroxymethyl]-5-(benzyloxycarbonylamino)pentyl]-L-proline amide, t-butoxycarbonyl-D-phenylalanyl-L-proline (255 mg, 0.70 mmol), 2-[2-amino-6-(benzyloxycarbonyl) amino-1-hydroxybenzotriazole (94mg, 0.70 mmol) and N-hydroxybenaotriazole (94 mg, 0.70 mmol) were dissolved in 15 ml of acetonitrile, 1-ethyl-3- (3'-dimethylaminopropyl)carbodiimide hydrochloride (160 mg, 0.84 mmol) was added under ice-cooled conditions, the mixture was stirred at this same temperature for 3 hours, the temperature was raised to room temperature and the mixture was then stirred for 15 hours. The reaction mixture was concentrated, after which it was dissolved in ethyl acetate. It was then washed with water, after which it was desiccated with $MgSO_4$. The solvent was removed, the crude product was refined by flash chromatography (ethyl acetate) and the target compound (393 mg, 81%) was obtained.

^{1}H-NMR($CDCl_3$) δ 1.20-2.15 (m, 20H), 2.40-2.80 (m, 1H), 2.90-3.47 (m, 3H) 3.65-3.77 (m, 1H), 4.23-4.58 (m, 3H), 4.95-5.04 (m, 2H), 5.04-5.30 (m, 2H), 5.30-5.56 (m, 2H) 7.04-7.90 (m, 12H).

[0050] (b) D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-5-aminopentyl]-L-proline amide

Oxalyl chloride (72 ml, 0.84 mmol) was dissolved in 3 ml of methylene chloride, dimethyl sulfoxide (119 ml, 1.68 mmol) was added at -40°C and the mixture was stirred for 5 minutes. 5 ml of methylene chloride solution containing the aforementioned compound (390 mg, 0.56 mmol) was added and the mixture was stirred for 30 minutes at -40 to -30°C. Next, triethylamine (394 ml, 2.81 mmol) was added and the mixture was stirred for 30 minutes at this same temperature, after which it was emptied into ice water. The organic layer was separated and washed with water, after which it was desiccated with $MgSO_4$ and concentrated. The product was refined by flash chromatography (hexane/ethyl acetate) and t-butoxycarbonyl-D-phenylalanyl-N-[1-[(2-thiazolyl) carbonyl]-5-(benzyloxycarbonyl)aminopentyl]-L-proline amide (388 mg, 73%) was obtained. This compound was dissolved in formic acid (3.5 ml), Pd (150 mg) was added and the mixture was stirred for 3 hours at room temperature. The reaction mixture was filtered, after which the filtrate was concentrated, the product was dissolved in 1 ml of anisole, trifluoroacetic acid (3 ml) was added under ice-cooled conditions and the mixture was stirred at this same temperature for 30 minutes. The reaction mixture was concentrated and was dissolved in 5 ml of water. It was then washed with water, after which freeze-drying was performed and the target substance (190 mg) was obtained.

^{1}H-NMR(D_2O) δ 1.25-2.04 (m, 7H), 2.04-2.18 (m, 1H), 2.64-2.82 (m, 2H), 3.00-3.70 (m, 6H), 4.30-4.45 (m, 2H), 5.45-5.55 (dd, J = 4.14, 9.31 Hz, 1H), 7.20-7.55 (m, 5H), 7.70-8.20 (m, 2H); MS(FD) m/z 458 (M^+).

[0051] (c) Synthesis of intermediate

The 2-[2-amino-6-(benzyloxycarbonyl)amino-1-hydroxyhexyl]thiazole that was used in this example was synthesized by the same method as in Example 1c using Nα-allyloxycarbonyl-Nω-bensyloxycarbonyl-L-lysine methyl ester as the starting substance.

^{1}H-NMR($CDCl_3$) δ 1.20-1.80 (m, 6H), 1.80-1.96 (m, 1H), 3.10-3.34 (m, 3H) 3.60-3.80 (m, 1H), 4.70 (d, J = 3.78 Hz, 1H), 4.80-4.97 (m, 1H), 5.01 (s, 2H), 7.29 (d, J = 2.52 Hz, 1H), 7.30-7.38 (m, 5H) 7.73 (d, J = 2.52 Hz, 1H).

[0052] Example 4

D-cyclohexylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized by the same method as in Example 1 from t-butoxycarbonyl-D-cyclohexylalanyl-L-proline and the compound of Example 1c.

^{1}H-NMR(D_2O) δ 1.00-1.55 (m, 4H), 1.55-2.25 (m, 14H), 2.30-2.40 (m, 1H), 3.22-3.30 (m, 2H), 3.58-3.70 (m, 1H), 3.72-3.82 (m, 1H), 4.39 (dd, J = 3.45, 13.8 Hz, 1H), 4.56 (dd, J=8.6 Hz, 1H), 4.80-5.80 (m, 1H), 8.10-8.23 m, 2H), MS(SIMS) m/z 492 (M^{+1}).

[00053] Example 5

D-phenylglycyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized by the same method as in Example 1 from t-butoxycarbonyl-D-phenylglycyl-L-proline and the compound of Example 1c.

^{1}H-NMR(D_2O) δ 1.62-1.97 (m, 8H), 2.10-2.20 (m, 1H), 2.98-3.06 (m, 1H), 3.22-3.30 (m, 1H), 3.63-3.72 (m, 1H), 4.58 (dd, J = 3.40, 8.60 Hz, 1H), 5.38-5.43 (m, 1H), 5.50-5.60 (m, 1H), 7.45-7.60 (m, 5H), 8.10 (d, 1H), 8.20 (d, 1H); MS(SIMS) m/z 472 (M^{+1}).

[0054] Example 6

D-tyrosyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized by the same method as in Example 1 from t-butoxycarbonyl-D-tyrosyl-L-proline and the compound of Example 1c.

^{1}H-NMR(D_2O) δ 1.75-2.04 (m, 6H), 2.16-2.36 (m, 2H), 3.04-3.10 (m, 1H), 3.25-3.28 (m, 6H), 3.45-3.46 (m, 1H), 3.70-3.76 (m, 1H) 4.52-4.77 (m, 2H), 5.52-5.56 (m, 1H), 6.85-6.96 (m, 2H), 7.19-7.26 (m, 2H), 8.13-8.19 (m, 2H), MS(SIMS) m/z 504 (M^{+1}).

[0055] Example 7

D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-octahydroindole-2-carboxyamide

It was synthesized by the same method as in Example 1 from t-butoxycarbonyl-D-phenylalanyl-L-octahydroindole-2-carboxylic acid and the compound of Example 1c.

^{1}H-NMR(D_2O) δ 0.87-1.05 (m, 2H), 1.10-1.23 (m, 3H), 1.36-1.49 (m, 3H), 1.58-1.82 (m, 5H), 1.91-2.03 (m, 2H), 2.85-3.00 (m, 2H), 3.15-3.20 (m, 3H), 4.20-4.25 (m, 1H), 4.34 (dd, J = 5.4, 10.3 Hz, 1H), 5.38 (dd, J = 4.0, 8.4 Hz, 1H), 7.19-7.36 (m, 5H), 7.98-8.04; MS(SIMS) m/z 540 (M^{+1}).

[0056] Example 8

Benzyloxycarbonyl-D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized in the same way as in Example 1 from benzyloxycarbonyl-D-phenylalanyl-L-proline and the compound of Example 1c.

^{1}H-NMR($CDCl_3$) δ 1.40-2.20 (m, 7H), 2.59-2.80 (m, 1H), 2.90-3.50 (m, 5H), 3.50-3.80 (m, 1H) 4.28-4.54 (m, 1H), 4.54-4.70 (m, 1H), 5.04 (ABq, J = 13.8, 39.7 Hz, 1H), 5.45-5.70 (m, 1H), 6.18-6.30 (m, 1H), 6.90-7.50 (m, 10H), 7.65 (d, J = 7.36 Hz, 1H), 7.84 (d, J = 7.36 Hz, 1H), 7.94-8.04 (m, 1H); MS SIMS m/z 620 (M^{+1}).

[0057] Example 9

Acetyl-D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized in the same way as in Example 1 from acetyl-D-phenylalanyl-L-proline and the compound of Example 1c.

^{1}H-NMR(D_2O) δ 1.50-2.50 (m, 11H), 2.52-2.75 (m, 2H), 2.97-3.13 (m, 2H), 3.15-3.50 (m, 2H), 3.65-3.80 (m, 1H), 4.35-4.50 (m, 1H), 5.35-5.50 (m, 1H), 7.23-7.56 (m, 5H), 8.00-8.22 (m, 2H), MS(SIMS) m/z 528 (M^{+1}).

[0058] Example 10

3-phenylpropionyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized by the same method as in Example 1 from 3-phenylpropionyl- L-proline and the compound of Example 1c

^{1}H-NMR(D_2O) δ 1.50-2.50 (m, 6H), 2.50-3.25 (m, 8H), 3.25-3.57 (m, 2H), 4.28-4.38 (m, 1H), 5.40-5.46 (m, 1H), 7.20-7.40 (m, 5H), 7.60-7.70 (m, 1H), 8.00-8.10 (m, 1H); MS(SIMS) m/z 471 (M^{+1}).

[0059] Example 11

4-phenylbutanoyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized in the same way as in Example 1 from 4-phenylbutanoyl-L- proline and the compound of Example 1c.

^{1}H-NMR($CDCl_3$) δ 1.72-1.75 (m, 2H), 1.89-2.09 (m, 5H), 2.26-2.51 (m, 5H), 2.61-2.68 (m, 2H), 3.13-3.56 (m, 4H) 4.42-4.53 (m, 1H), 5.59 (brs, 1H), 7.08-7.28 (m, 5H), 7.70 (d, J = 3.1 Hz, 1H), 7.77-7.90 (m, 2H), 8.00 (d, J = 3.1 Hz, 1H), MS(SIMS) m/z = 485 (M^{+1}).

[0060] Example 12

D-propyl-N-[1-[(2-thiazolyl)carbonyl]-4-guanidinobutyl]-L-proline amide

It was synthesized in the same way as in Example 1 from t-butoxycarbonyl- D-pyrrolyl-L-proline and the compound of Example 1c.

^{1}H-NMR(D_2O) δ 1.70-2.20 (m, 9H), 2.30-2.45 (m, 1H), 2.47-2.65 (m, 2H), 3.25-3.35 (m, 1H), 3.40-3.55 (m, 2H), 3.60-3.68 (m, 1H), 3.70-3.80 (m, 1H), 3.80-3.90 (m, 1H), 4.58 (dd, J = 3.40, 5.17 Hz, 1H), 4.68 (dd, J = 6.90, 7.59 Hz, 1H), 5.51 (dd, J = 5.17, 9.31 Hz, 1H), 8.12 (d, J = 3.40 Hz, 1H), 8.18 (d, J = 3.40 Hz, 1H); MS(FD) m/z 435 (M^+).

[0061] Example 13

2-[2-(phenylthioacetyl)cyclohexa-1-ylcarbonyl-L-arginyl]thiazole

It was synthesized in the same method as in Example 2 from 2-(phenylthioacetyl)cyclohexanecarboxylic acid and the compound from Example 1c.

^{1}H-NMR(CD_3OD) δ 1.10-2.20 (m, 12H), 2.63 (m, 1H), 3.02 (m, 1H), 3.09-3.23 (m, 2H), 3.83-4.09 (m, 2H), 5.47-5.55 (m, 1H), 7.05-7.40 (m, 5H), 8.02 (m, 1H), 8.10 (m, 1H); MS(SIMS) m/z 502 (M^{+1}).

[0062] Example 14

4-phenylbutanoyl-N-[1-[(2-thiazolyl)carbonyl]-5-aminopentyl]-L-proline amide

It was synthesized in the same method as in Example 3 from 4-phenylbutanoyl-L-proline and the compound of Example 3c.

^{1}H-NMR(D_2O) δ 1.40-2.25 (m, 10H), 2.35 (m, 2H), 2.65 (m, 2H), 2.99 (m, 2H), 3.42-3.52 (m, 4H), 4.40 (m, 1H), 5.46 (m, 1H), 7.10-7.40 (m, 5H), 8.05 (m, 1H), 8.11 (m, 1H); MS(SIMS) m/z 457 (M^{+1}).

[0063] Example 15

3-phenylpropionyl-N-[1-[(2-thiazolyl)carbonyl]-5-aminopentyl]-L-proline amide

It was synthesized in the same method as in Example 3 from 3-phenylpropionyl-L-proline and the compound of Example 3c.

^{1}H-NMR(D_2O) δ 1.20-1.90 (m, 7H), 1.90-2.20 (m, 2H), 2.50-3.00 (m, 5H), 3.20-3.54 (m, 2H), 4.29-4.37 (m, 1H), 5.39 (dd, J = 3.75, 8.00 Hz, 1H), 7.12-7.35 (m, 5H), 7.98 (d, J = 2.77 Hz, 1H), 8.06 (d, J = 2.77 Hz, 1H): MS(SIMS) m/z 443 (M^{+1}).

[0064] Example 16

D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-6-aminohexyl]-L-proline amide

It was synthesized in the same method as in Example 3 from t-butoxycarbonyl-D-phenylalanyl-L-proline and 2-[2-amino-7-(benzyloxycarbonyl) amino-1-hydroxypentyl]thiazole.

^{1}H-NMR(D_2O) δ 1.20-1.90 (m, 9H), 2.00-2.20 (m, 2H), 2.74 (ddd, J = 6.90, 7.24, 7.59 Hz, 1H), 2.98-3.10 (m, 2H), 3.10-3.32 (m, 2H), 3.39-3.50 (m, 1H), 4.44 (dd, J = 4.83, 9.66 Hz, 1H), 4.50-4.60 (m, 1H), 5.48 (dd, J = 4.14, 9.66 Hz, 1H), 7.25-7.50 (m, 5H), 8.10 (d, J = 2.41 Hz, 1H), 8.15 (d, J = 2.41 Hz, 1H): MS(SIMS) m/z 471 (M^{+1}).

[0065] Example 17

3-phenylpropionyl-N-[1-[(2-thiazolyl)carbonyl]-6-aminohexyl]-L-proline amide

It was synthesized in the same method as in Example 3 from 3-phenylpropionyl-L-proline and 2-[2-amino-7-(benzyloxycarbonyl) amino-1-hydroxyheptyl]thiazole

^{1}H-NMR(D_2O) δ 1.20-1.90 (m, 10H), 1.90-2.08 (m, 1H), 2.08-2.30 (m, 1H), 2.54-2.85 (m, 1H), 2.85-3.06 (m, 6H), 3.25-3.35 (m, 1H), 3.40-3.61 (m, 2H), 4.41 (d, J = 6.90 Hz, 1H), 5.43 (dd, J = 3.45, 8.60 Hz, 1H), 7.14-7.37 (m, 5H), 8.02 (d, J = 24 Hz, 1H), 8.08 (d, J = 24 Hz, 1H): MS(FD) m/z 456 (M^+).

[0066] Example 18

D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-methoxybutyl]-L-proline amide

It was synthesized in the same method as in Example 1 from t-butoxycarbonyl-D-phenylalanyl-L-proline and 2-2(-amino-1-hydroxy-5-methoxypentyl)thiazole.

^{1}H-NMR($CDCl_3$) δ 1.57-1.59 (m, 1H), 1.73-1.88 (m, 5H), 2.07-2.14 (m, 2H), 2.75-2.78 (m, 1H), 3.20-3.33 (m, 2H), 3.35 (s, 3H), 3.49-3.56 (m, 3H), 4.42 (dd, J = 4.2, 8.5 Hz, 1H), 4.53 (m, 1H), 5.49 (dd, J = 4.3, 8.4 Hz, 1H), 7.31-7.34 (m, 2H), 7.41-7.46 (m, 3H), 8.09 (d, J = 3.1 Hz, 1H), 8.14 (d, J = 3.1 Hz, 1H), MS(FD) m/z = ~~459~~ (M^{+1}).

[0067] Example 19

D-phenylalanyl-N-[1-[(2-benzothiazolyl)carbonyl]-4-methoxybutyl]-L-proline amide

It was synthesized in the same method as in Example 1 from t-butoxycarbonyl-D-phenylalanyl-L-proline and 2-2(-amino-1-hydroxy-5-methoxypentyl)benzothiazole.

^{1}H-NMR($CDCl_3$) δ 1.74-1.78 (m, 1H), 1.80-1.93 (m, 4H), 2.04-2.19 (m, 2H), 2.73-2.74 (m, 1H), 3.15-3.28 (m, 2H), 3.35 (s, 3H), 3.54-3.58 (m, 4H), 4.40-4.45 (m, 1H), 4.50-4.54 (m, 1H), 5.56 (dd, J = 4.3, 8.4 Hz, 1H), 7.24-7.43 (m, 5H), 7.67-7.73 (m, 2H), 8.15-8.26 (m, 2H); MS(SIMS) m/z = 509 (M^{+1}).

[0068] Example 20

t-butoxycarbonyl-D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-4-methoxybutyl]-L-proline amide

It was synthesized from t-butoxycarbonyl-D-phenylalanyl-L-proline and 2-(2-amino-1-hydroxy-5-methoxypentyl)thiazole and was obtained as the intermediate of Example 18.

^{1}H-NMR(D_2O) δ 1.51-1.90 (m, 14H), 2.15-2.23 (m, 2H), 2.62-2.66 (m, 1H), 3.01-3.04 (m, 2H), 3.30 (s, 3H), 3.38-3.44 (m, 3H), 3.54-3.57 (m, 1H), 4.49-4.62 (m, 2H), 5.40-5.43 (m, 1H), 5.75-5.79 (m, 1H), 7.18-7.32 (m, 5H), 7.53-7.61 (m, 2H), 7.95-7.98 (m, 1H), 8.18-8.21 (m, 1H); MS(FD) m/z 558 (M^+).

[0069] Example 21

t-butoxycarbonyl-D-phenylalanyl-N-[1-[(2-benzothiazolyl)carbonyl]-4-methoxybutyl]-L-proline amide

It was synthesized from t-butoxycarbonyl-D-phenylalanyl-L-proline and 2-(2-amino-1-hydroxy-5-methoxypentyl)benzothiazole and was obtained as the intermediate of Example 19.

^{1}H-NMR(D_2O) δ 1.43 (s, 9H), 1.51-1.67 (m, 4H), 1.80-1.89 (m, 2H), 2.07-2.21 (m, 2H), 2.61-2.63 (m, 1H), 2.90-3.05 (m, 2H), 3.30 (s, 3H), 3.33-3.40 (m, 2H), 3.51-3.54 (m, 1H), 4.44-4.68 (m, 1H), 4.62-4.64 (m, 1H), 5.44-5.47 (m, 1H), 5.55-5.62 (m, 1H), 7.20-7.31 (m, 5H), 7.63-7.65 (m, 1H), 7.68 (d, J = 3.0 Hz, 1H), 8.02 (d, J = 3.0 Hz, 1H); MS(FD) m/z 608 (M^+).

[0070] Example 22

D-phenylalanyl-N-[1-[(2-thiazolyl)carbonyl]-2-phenylethyl]-L-proline amide

It was synthesized by the same method as in Example 1 from t-butoxycarbonyl-D- phenylalanyl-L-proline and 2-(2-amino-1-hydroxy-3-phenylpropyl)thiazole.

^{1}H-NMR($CDCl_3$) δ 1.49-1.54 (m, 2H), 1.60-1.80 (m, 1H), 2.10-2.14 (m, 1H), 2.59-2.67 (m, 1H), 2.85-2.97 (m, 2H), 3.10-3.19 (m, 1H), 3.28-3.49 (m, 2H), 3.64-3.75 (m, 1H), 4.50-4.54 (m, 1H), 5.88-5.93 (m, 1H), 7.20-7.36 (m, 10H), 7.67-7.78 (m, 2H), 8.06-8.08 (m, 1H); MS(SIMS) m/z = 477 (M^{+1}).

[0071] Example 23

4-phenylbutanoyl-N-[1-[(2-thiazolyl)carbonyl]ethyl]-L-proline amide

It was synthesized by the same method as in Example 1 from 4-phenylbutanoyl-L-proline and 2-(2-amino-1-hydroxypropyl)thiazole.

^{1}H-NMR($CDCl_3$) δ 1.52 (d, J = 6.90 Hz, 1H), 1.80-2.30 (m, 6H), 2.30-2.38 (m, 2H), 2.68-2.74 (m, 2H), 3.30-3.40 (m, 1H), 3.45-3.52 (m, 1H), 4.62 (dd, J = 2.41, 9.31 Hz, 1H), 5.69 (q, J = 6.90 Hz, 1H), 7.18-7.31 (m, 5H), 7.69 (d, J = 3.10 Hz, 1H), 8.02 (d, J = 3.10 Hz, 1H); MS(FD) m/z = 399 (M^+).

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最終頁に続く

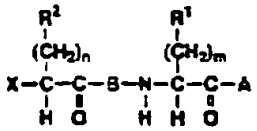
(54)【発明の名称】　トロンビン阻害作用を有する複素環カルボニル化合物

(57)【要約】

【目的】

【構成】　本発明は、トロンビンに対し阻害活性を有し、血栓症の予防や治療に用いられる一般式（Ｉ）で表される化合物並びにその薬理学上許容される塩に関する。

【化１８】



(I)

[式中、Ａは複素環式基、Ｒ¹はアルキル基、グアニジノ基、アミジノ基、アミジノチオ基、アミノ基、水酸基、メルカプト基、低級アルコキシ基、置換されていてもよいフェニル基、Ｂはアミノ酸残基、Ｒ²はメチル基、シクロアルキル基、アリール基、ヘテロアリール基、アリールチオ基、Ｘは水素原子、水酸基、アミノ基、ハロゲン原子、アルキルアミノ基、アシルアミノ基、アルコキシカルボニルアミノ基、ｍは１～５の整

(19)日本国特許庁（ＪＰ）　(12) 公開特許公報（A）　(11)特許出願公開番号

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(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ	技術表示箇所
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(72)発明者　小此木　恒夫
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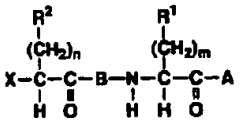
(54)【発明の名称】　トロンビン阻害作用を有する複素環カルボニル化合物

(57)【要約】

【目的】

【構成】　本発明は、トロンビンに対し阻害活性を有し、血栓症の予防や治療に用いられる一般式（Ｉ）で表される化合物並びにその薬理学上許容される塩に関する。

【化１８】



(I)

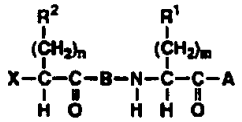
［式中、Ａは複素環式基、Ｒ[1]はアルキル基、グアニジノ基、アミジノ基、アミジノチオ基、アミノ基、水酸基、メルカプト基、低級アルコキシ基、置換されていてもよいフェニル基、Ｂはアミノ酸残基、Ｒ[2]はメチル基、シクロアルキル基、アリール基、ヘテロアリール基、アリールチオ基、Ｘは水素原子、水酸基、アミノ基、ハロゲン原子、アルキルアミノ基、アシルアミノ基、アルコキシカルボニルアミノ基、ｍは１～５の整数、ｎは０～４の整数をそれぞれ示す］

1

【特許請求の範囲】

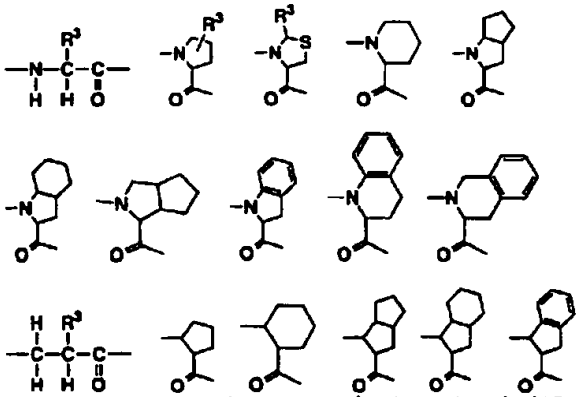
【請求項１】　下記の一般式（I）で表される複素環カルボニル化合物およびその薬理学的に許容される塩。

【化１】



(I)

[式中、Ａは少なくとも1個の窒素原子を有する５員環もしくは６員環の飽和、部分飽和または不飽和である単環式複素環、またはベンゼン環もしくはピリジン環が縮合している二環式複素環（上記複素環は酸素原子、イオウ原子または別途３個以下の窒素原子を有してもよく、＊



（R^3は水素、炭素数１～６の分岐してもよいアルキル基、フェニル基、フェニルメチル基である）を示し、R^2はメチル基、アリール基、シクロアルキル基、ヘテロアリール基、アリールチオ基、Ｘと結合しているメチレンを示し、Ｘは水素原子、水酸基、アミノ基、ハロゲン原子、炭素数１～４のアルキルアミノ基、アシルアミノ基、アルコキシカルボニルアミノ基、アリールオキシカルボニルアミノ基を示し、ｍは１～５の整数を示し、ｎは0～４の整数を示す。]

【請求項２】請求項１の一般式（Ｉ）において、Ａはチアゾール、オキサゾール、イミダゾール、チアゾリン、オキサゾリン、イミダゾリン、ピリジン、ピリミジン、ピラゾール、1,2,4-チアジアゾール、1,2,4-オキサジア※

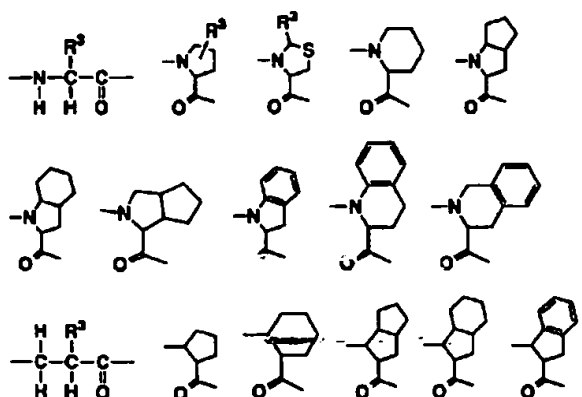
2

＊単環式複素環では環内の炭素原子または二環式複素環ではベンゼン環もしくはピリジン環の炭素原子に炭素数１～４の低級アルキル基、ハロゲン、水酸基、アミノ基、メルカプト基で置換してもよく、また複素環を構成している何れかの炭素原子を介してカルボニル基に結合している）を示し、R^1は炭素数１～４の分岐してもよいアルキル基、グアニジノ基、アミジノチオ基、アミジノ基、アミノ基、水酸基、メルカプト基、低級アルコキシ基、もしくはグアニジノ基、アミジノ基、アミノ基、水酸基、メルカプト基、ハロゲンで置換されてもよいフェニル基を示し、Ｂは以下から選択される残基

【化２】

※ゾール、1,2,4-トリアゾール（上記複素環は構成している何れかの炭素原子を介してカルボニル基に結合している）、ベンゾチアゾール、ベンゾオキサゾール、ベンゾイミダゾール、チアゾロ[5,4-b]ピリジン、オキサゾロ[4,5-b]ピリジン、イミダゾ[4,5-b]ピリジン（上記複素環は２位の炭素原子を介してカルボニル基に結合している）を示し、R^1はグアニジノ基、アミジノチオ基、アミジノ基、アミノ基、水酸基、メルカプト基、低級アルコキシ基、もしくはグアニジノ基、アミジノ基、アミノ基、水酸基、メルカプト基、ハロゲンで置換されてもよいフェニル基を示し、Ｂは以下の式から選択される残基

【化３】



（R^3は一般式(I)で定義したものと同じ意味を表す）を示し、R^2はメチル基、置換基を有してもよいフェニル基、チエニル基、ピリジル基、インドリル基、ナフチル基、ジフェニルメチル基、シクロペンチル基、シクロヘ

3

キシル基、フェニルチオ基、Xと結合しているメチレンを示し、Xは水素原子、水酸基、アミノ基、ハロゲン原子、炭素数1～4のアルキルアミノ基、アシルアミノ基、アルコキシカルボニルアミノ基、アリールオキシカルボニルアミノ基を示し、mは1～5の整数を示し、nは0～4の整数を示す複素環カルボニル化合物。

【請求項3】請求項1または請求項2に記載の複素環カルボニル化合物または薬理学的に許容されるそれらの塩を有効成分として含有するトロンビン阻害剤。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明はトロンビン阻害作用を有する新規な複素環カルボニル化合物に関する。

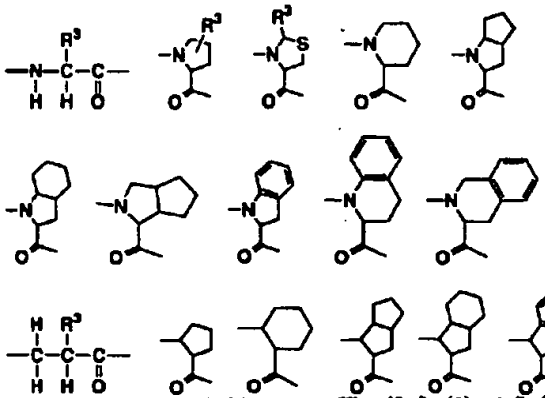
【0002】

【従来の技術】トロンビン阻害作用を示す化合物としては、例えば特開昭54－100342、米国特許第4399065号、4927809号等に記載のものが知られている。　しかしながらこれら従来の化合物はトロンビン阻害活性が十分ではなく、より高い活性と酵素選択性を有する化合物が求められているといえる。

【発明の概要】

【0003】

【発明が解決しようとする課題】本発明者はプロテアーゼ阻害剤の研究からトロンビン阻害作用を有する一群の新規化合物を見いだした。　従って本発明はトロンビン阻害作用を有する新規な複素環カルボニル化合物を提供することを目的としている。　また本発明はトロンビン阻害作用を有する新規な複素環カルボニル化合物を有効成分として含有するトロンビン阻害剤の提供をその目的＊



（R^3は一般式（I）で定義したものと同じ意味を表す）を示し、R^2は置換されてもよいフェニル基、チエニル基、ピリジル基、インドリル基、ナフチル基、ジフェニルメチル基、シクロペンチル基、シクロヘキシル基、フェニルチオ基、Xと結合しているメチレンを示し、Xは水素、水酸基、アミノ基、炭素数1～4のアルキルアミノ基、アシルアミノ基、アリールオキシカルボニルアミノ基、アルコキシカルボニルアミノ基を示し、mは1～5の整数を示し、nは0～4の整数を示す。］

また本発明によるトロンビン阻害剤および抗凝固剤は前

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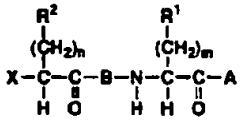
＊としている。

【0004】

【課題を解決するための手段】本発明による複素環カルボニル化合物は下記の一般式（1）で表される化合物およびその薬理学的に許容される塩である。

【0005】

【化4】



(I)

［式中、Aは少なくとも1個窒素原子を有する5員環もしくは6員環の飽和、部分飽和または不飽和である単環式複素環、またはベンゼン環もしくはピリジン環が縮合している二環式複素環（上記複素環は酸素原子、イオウ原子または別途3個以下の窒素原子を有してもよく、単環式複素環では環内の炭素原子または双環式複素環ではベンゼン環もしくはピリジン環の炭素原子に炭素数1～4の低級アルキル基、ハロゲン、水酸基、アミノ基、メルカプト基で置換してもよく、また複素環を構成している何れかの炭素原子を介してカルボニル基に結合している）を示し、R^1は炭素数1～6の分岐してもよいアルキル基、グアニジノ基、アミジノチオ基、アミジノ基、アミノ基、水酸基、メルカプト基、低級アルコキシ基、もしくはグアニジノ基、アミジノ基、アミノ基、水酸基、メルカプト基、ハロゲン原子で置換されてもよいフェニル基を示し、Bは以下から選択される残基

【0006】

【化5】

記一般式（I）の化合物と薬理学上許容される塩を含んでなるものである。本発明による上記一般式（I）の化合物は強いトロンビン阻害活性を有し、医薬として有用である。

【0007】［発明の具体的説明］一般式（i）においてAが表す置換基としては1個の窒素原子を有する5員環もしくは6員環の飽和、部分飽和である単環式複素環、またはベンゼン環もしくはピリジン環が縮合している二環式複素環（上記複素環は酸素原子、イオウ原子または別途3個以下の窒素原子を有してもよく、単環式複

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素環では環内の炭素原子または二環式複素環ではベンゼン環もしくはピリジン環の炭素原子に炭素数1～4の低級アルキル基、ハロゲン、水酸基、アミノ基、メルカプト基で置換してもよく、また複素環を構成している何れかの炭素原子を介してカルボニル基に結合している）である。　好ましくはチアゾール、オキサゾール、イミダゾール、チアゾリン、オキサゾリン、イミダゾリン、ピリジン、ピリミジン、ピラゾール、1,2,4-チアジアゾール、1,2,4-オキサジアゾール、1,2,4-トリアゾール（上記複素環は構成している何れかの炭素原子を介してカルボニル基に結合している）等の単環式複素環、もしくはベンゾチアゾール、ベンゾオキサゾール、ベンゾイミダゾール、チアゾロ[5,4-b]ピリジン、オキサゾロ[4,5-b]ピリジン、イミダゾ[4,5-b]ピリジン（上記複素環は2位の炭素原子を介してカルボニル基に結合している）等の二環式複素環である。

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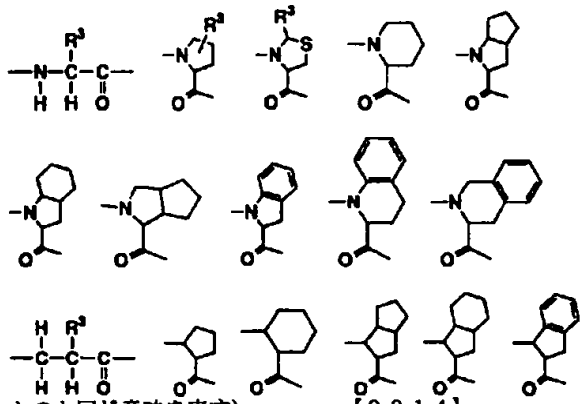
＊【0008】また一般式（I）においてR¹が表す置換基としてはメチル基、イソプロピル基、グアニジノ基、アミジノチオ基、アミジノ基、アミノ基、水酸基、メルカプト基、低級アルコキシ基、或はグアジニノ基、アミジノ基、アミノ基、水酸基、メルカプト基、ハロゲン原子で置換されてもよいフェニル基であり、mは1～5の整数である。　好ましくはR¹はグアニジノ基、アミジノ基、アミノ基、もしくはグアニジノ基、アミジノ基、アミノ基で置換されたフェニル基であり、mは3～5の整数である。

【0009】また一般式（I）においてBが表す残基としてはα-アミノ酸、イミノ酸残基あるいは直鎖状または環状カルボニル化合物である。　好ましくは下記構造式から選択される残基があげられる。

【0010】

【化6】



（R³は一般式（I）で定義したものと同じ意味を表す）

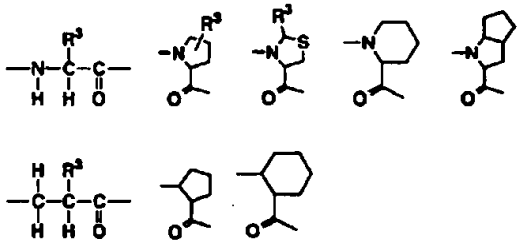
【0011】また一般式（I）においてR²が表す置換基としては分岐してもよいアルキル基、アリール基、置換してもよいフェニル基、シクロアルキル基、窒素原子を1または2個含む複素飽和（芳香）環、酸素原子または硫黄原子を一個含む5または6員の複素飽和（芳香）環であり、Xと結合しているメチレンであり、nは0～5の整数である。　好ましくはR²がフェニル基、ジフェニルメチル基、ビフェニル基、ナフチル基、ピリジル基、ピロール基、インドリル基、チエニル基、フラニル基、フェニルチオ基、Xと結合しているメチレンで形成される複素環としてはピロリジン、ピペリジンであり、nは0～2の整数である。

【0012】また一般式（I）においてXが表す置換基としては水素、ハロゲン、水酸基、アミノ基、アルキルアミノ基、アシルアミノ基、アルコキシカルボニルアミノ基である。　好ましくはアミノ基、メチルアミノ基、アセチルアミノ基、フェニルアセチルアミノ基、ベンジルオキシカルボニルアミノ基、t-ブトキシカルボニルアミノ基等が挙げられる。

【0013】本発明の好ましい化合物群としては、一般式（I）において、Aがチアゾール、R¹がグアニジノ基、Bが次の構造式から選択される残基であり、

【0014】

【化7】



（R³は一般式(I)で定義したものと同じ意味を表す）、R²がアリール基、シクロアルキル基もしくはフェニルチオ基、Xが水素、アミノ基もしくはベンジルオキシカルボニルアミノ基、mが3、nが0もしくは1である化合物、Aがチアゾール、R¹がアミノ基、Bが次の構造式から選択される残基であり、

【0015】

【化8】

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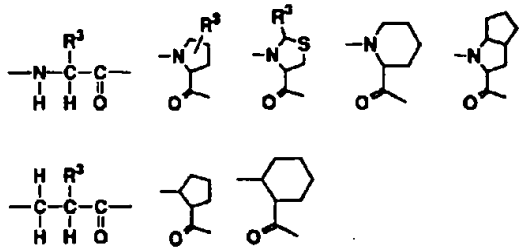

（R^3は一般式(I)で定義したものと同じ意味を表す）、R^2がアリール基、シクロアルキル基もしくはフェニルチオ基、Xが水素、アミノ基もしくはベンジルオキシカルボニルアミノ基、mが4もしは5、nが0もしくは1である化合物が挙げられる。

【0016】さらに、本発明の好ましい具体的化合物としては、例えば、D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド、D-シクロヘキシルアラニル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド、D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-オクタヒドロインドール-2-カルボキシアミド、D-フェニルグリシル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド、(ベンジルオキシカルボニル)-D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド、アセチル-D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド、フェニルプロピオニル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド、2-[N-[2-(フェニルチオアセチル)シクロペンタ-1-イルカルボニル]-L-アルギニル]チアゾール、D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-5-アミノペンチル]-L-プロリンアミド、D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-6-アミノヘキシル]-L-プロリンアミドなどが挙げられる。

【0017】本発明による化合物は分子中の炭素原子に由来する立体異性体が存在し得るが、いずれの異性体も本発明に包含されるものである。本発明による化合物はその塩とすることができる。　そのような塩としては、薬理学上許容される塩が挙げられ、好ましくは塩化水素酸、臭化水素酸、ヨウ化水素酸、硝酸、硫酸、リン酸、酢酸、クエン酸、マレイン酸、コハク酸、乳酸、酒石酸、メタンスルホン酸、エタンスルホン酸、ベンゼンスルホン酸、p-トルエンスルホン酸等が挙げられる。

【0018】一般式（I）の化合物は種々の方法で合成することができる。例えば、次の一般式（II）

【0019】

【化9】

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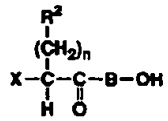
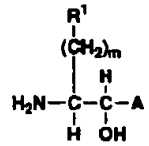
 　(II)

（ここで、R^2，X，B，nは一般式（I）で定義したものとおなじ意味を表す、かつXは保護基を有する基を表す）で表される化合物と、次の一般式（III）

【0020】

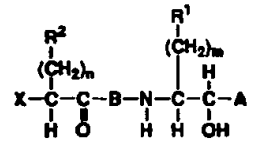
【化10】

 　(III)

（ここで、R^1，A，mは一般式（I）で定義したものとおなじ意味を表す、かつR^1は保護基を有する基を表す。）で表される化合物とを、適当なカップリング試薬と反応することによって次の一般式（IV）

【0021】

【化11】

 　(IV)

（ここで、R^1，R^2，A，B，X，m，nは前記で定義したものとおなじ意味を表す）の化合物を得ることができる。　合成上、R^1およびXに保護基を必要とする場合には一般的にペプチド化学で用いられる保護基を用いることができる。　好ましくはt-ブトキシカルボニル基、ベンジルオキシカルボニル基、4-メトキシ-2,3,6-トリメチルベンゼンスルホニル基等を挙げることができる。

【0022】カップリング試薬はペプチド化学で用いられる試薬を使用することができる。好ましいカップリング試薬は例えばN,N'-ジシクロヘキシルカルボジイミド、1-エチル-3-（3'-ジメチルアミノプロピル）カルボジイミド、ベンゾトリアゾール-1-イルオキシトリス（ジメチルアミノ）ホスホニウムヘキサフルオロホスフェート、N,N'-ビス［2-オキソ-3-オキサゾリジニル］ホスホロジアミド酸クロライド、ジフェニルホスフィニルクロライドである。　これらの試薬存在下に、適当な溶媒（例えば、酢酸エチル、アセトニトリル、塩化メチレン、DMF)中で、-70～30℃、好ましくは-20～10℃で反応を行うことができる。

【0023】次いで化合物（IV）の水酸基を酸化してケトンとし、必要によって保護基を除去し、一般式（I）の複素環カルボニル化合物を得ることができる。　酸化反応はシンセシス(Synthesis）1990年、857頁に記載のように種々の添加物を用いたジメチルスルホキシ

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ドにより行うことができる。　またテトラ-n-プロピルアンモニウム パールテネイト、ピリジニウム ジクロメイト、ピリジニウムクロロクロメイトによっても酸化することができる。　好ましくはオキザリルクロライドの存在下ジメチルスルホキシドによる酸化であり、例えば塩化メチレンを溶媒として-７０～０℃でオキザリルクロライドとジメチルスルホキシドから調製した試薬と化合物（IV)とを反応させ、次いでトリエチルアミンで処理することによって一般式（I）の化合物を得ることができる。

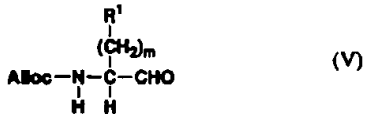
【００２４】一般式（I）の化合物を得るために、脱保護反応を必要とする場合には穏和な反応条件が選択される。　例えば前述の保護基が用いられた場合にはパラジウム炭素を触媒とする水素化分解もしくはアニソール、チオアニソール存在下トリフルオロ酢酸を作用させる酸分解反応で脱保護が行われる。

【００２５】本発明の一般式（I）の化合物は種々の無機酸または有機酸と酸付加塩を形成する。　上記反応で得られる化合物（I）は遊離の形態または塩の形態で単離され、遊離の形態の場合には所望の酸と反応させることにより酸付加塩を得ることができる。

【００２６】出発物質である上記アミン化合物（III）を得るためにはケミカルレビュー(Chemical Review)１９８９年、８９巻、１４９頁に記載の方法で得られるアミノアルデヒド化合物（V）

【００２７】

【化１２】



(V)

（R^1，mは一般式（II）で定義したものとおなじ意味を、Allocはアリルオキシカルボニル基を表す）を、ジャーナル・オブ・ヘテロサイクリック・ケミストリー(Journal of Heterocyclic Chemistry)　１９７１年、８巻、２５７頁、ジャーナル・オブ・オーガニック・ケミストリー(Journal of Organic Chemistry)１９８８年、５３巻、１７４８頁等に記載のシリル化合物（VIa)

【００２８】

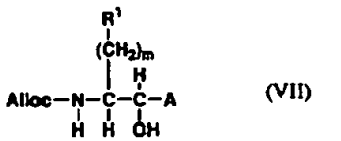
【化１３】

(VIa)

（Aは一般式（I）で定義したものとおなじ意味を表す）と反応させカルビノール化合物（VII）

【００２９】

【化１４】



(VII)

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を得ることができる。　好ましくはこの反応は塩化メチレンを溶媒としてフッ化セシウム、テトラブチルアンモニウムフルオライドの存在下もしくは非存在下０～５０℃の温度で反応を行うことができる。もしくは出発物質である複素環化合物（H-A）を不活性溶媒（例えばテトラヒドロフラン、ジメトキシエタン）中、n-ブチルリチウム等の塩基で処理し、化合物(VIb)

【００３０】

【化１５】

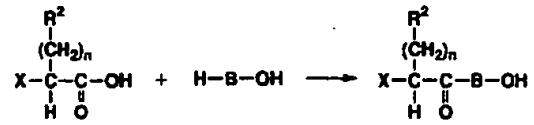
(VIb)

として、次いで上記化合物（V）と反応させ化合物（VII）を得ることができる。化合物（VII）のアミノ基保護基を公知の方法である、例えば$Pd(Ph_3P)_4$存在下、ピロリジンで処理し除去することにより上記アミン化合物（III）を得ることができる。

【００３１】また出発物質である上記カルボン酸化合物(II)はB-OHがアミノ酸残基の場合にはペプチド化学の一般的方法で得ることができる。　カルボン酸化合物（VIII）を反応性誘導体（例えば酸ハライド、酸無水物、活性エステル）に導き、アミノ酸(IX)のアルカリ金属塩もしくは有機塩基との塩と反応させることにより化合物(II)を得ることができる。　好ましくは化合物（VIII）をN-ヒドロキシコハク酸イミドと反応させ活性エステルに変換し、それを有機塩基の存在下にアミノ酸(IX)と反応させてペプチド結合を形成することによって行われる。

【００３２】

【化１６】



(VIII)　(IX)　(II)

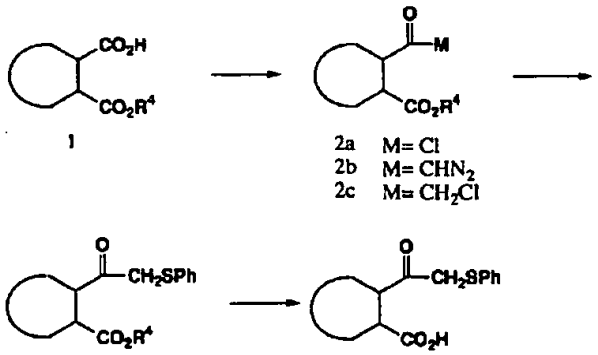
また上記化合物(II)のB-OHが脂肪族カルボン酸の場合には環状または直鎖状ジカルボン酸から得ることができる。　例えば環状ジカルボン酸では、そのモノアルキルエステル(1)をチオニルクロライドもしくはオキザリルクロライドと反応させ酸クロライド(2a)とし、これをジアゾメタンで処理してジアゾメチルケトン(2b)に変換する。　このケトンを無水塩化水素と反応させクロルメチルケトン(2c)とし、次いでチオフェノールで処理することによってフェニルチオメチルケトン(3)に変換する。

この化合物のエステルを加水分解し、カルボン酸化合物（II）を得ることができる。

【００３３】

【化１７】

11　　12



1　　2a M=Cl　2b M=CHN$_2$　2c M=CH$_2$Cl

3　　II

（R^{4}はメチル基、ベンジル基、ジフェニルメチル基を表す）

【００３４】本発明の化合物（I）およびその酸付加塩はトロンビンに対して選択性の高い阻害作用を示すことから血中のトロンビンを測定する診断薬、血小板凝集阻止剤あるいは血栓症の予防および治療に有用である。

【００３５】本発明による一般式（I）で表される化合物およびその薬理学的に許容される塩を有効成分として含有するトロンビン阻害剤は、経口または非経口投与（例えば、吸入投与、点鼻、点眼、皮下投与、静注、筋注など）に適した種々の剤形で使用される。

【００３６】例えば、その用途に応じて、錠剤、カプセル剤、顆粒剤、散剤、細粒剤、トローチ剤、シロップ剤、乳濁剤などの経口剤、吸入剤、点鼻剤、点眼剤などの外用液剤、静注および筋注などの注射剤などの製剤形態に調製することができる。これらの各種製剤は、通常用いられている賦形剤、増量剤、結合剤、湿潤化剤、崩壊剤、潤滑剤、分散剤、緩衝剤、保存剤、溶解補助剤、防腐剤、安定化剤などを用いて常法により製造することができる。

【００３７】薬剤中における本発明の化合物の含有量はその剤形に応じて異なるが、通常全組成物中１～７０重量％、好ましくは５～５０重量％である。またその投与量は用法、患者の年齢、性別、症状の程度などを考慮して＊て適宜決定されるが、通常成人１日当たり約０．１～２０００ｍｇ、好ましくは５～４００ｍｇ程度とするのがよく、これを１日１回または数回に分けて投与することができる。

【００３８】in vitro 阻害活性の測定方法

in vitro の系におけるトロンビン阻害活性はヨーロピアン・ジャーナル・オブ・バイオケミストリー(European Journal of Biochemistry)１９８８年、１７２巻、１７頁に記載の方法により求めた。0.1Mトリス塩酸緩衝液(pH 8.0; 0.3 M NaClおよび2 mM $CaCl_2$を含有) 100 ml、本発明化合物のDMSO溶液 10 ml、牛血清アルブミン溶液(0.4 mg/ml) 50 mlおよび上記トリス塩酸緩衝液に溶解したトロンビン(0.5 U/ml) 20 mlの混合液を調製した。　これに基質である5 mM Boc-Asp(OBzl)-Pro-Arg-メチルクマリンアミド溶液 (10%DMSO) 20 mlを加え、37℃で30分間インキュベートしたのち、380nmのUVで励起された440 nmの蛍光強度 (a_1) を測定した。同時に、本発明化合物溶液をDMSOに代えた実験を行い、同様に蛍光強度 (a_2) を測定した。またバックグラウンドとして上記0.1Mトリス塩酸緩衝液 120 ml、DMSO溶液 10 ml、牛血清アルブミン溶液 50 mlおよび基質溶液 20mlの混合液の蛍光強度(b)を測定した。　阻害率を次式より計算し、50%阻害に必要な濃度(IC_{50})を求めた。

$$阻害率\ (\%) = [[(a_2-b) - (a_1-b)] / (a_2-b)] \times 100$$

本発明の代表的化合物についてこの試験結果を表１に示す。

表１　トロンビン阻害活性

化合物の実施例番号	５０％阻害濃度 IC_{50} (μM/ml)
1	0.0015
2	0.16
4	0.012
5	0.32
7	0.007
8	0.002
アルガトロバン*	0.065

＊特公昭61-48829記載の化合物

【0039】

【実施例】本発明の化合物について以下に実施例を挙げて詳しく説明するが、これらは単なる例示であってなんら本発明を限定するものではない。

【0040】実施例1

D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド

(a) t-ブトキシカルボニル-D-フェニルアラニル-N-[1-[(2-チアゾリル)ヒドロキシメチル]-4-[[N',N"-ビス(t-ブトキシカルボニル)アミノイミノメチル]アミノ]ブチル]-L-プロリンアミド

t-ブトキシカルボニル-D-フェニルアラニル-L-プロリン(300 mg, 0.82 mmol)、2-[2-アミノ-5-[N', N"-ビス(t-ブトキシカルボニル)アミノイミノメチル]アミノ-1-ヒドロキシペンチル]チアゾール(367 mg, 0.82 mmol)、N-ヒドロキシベンゾトリアゾール(110 mg, 0.82 mmol)をアセトニトリル15 mlに溶解し、氷冷下1-エチル-3-(3'-ジメチルアミノプロピル)カルボジイミド塩酸塩(187 mg, 0.98mmol)を加え、同温度で3時間、室温まで昇温して15時間撹拌した。　反応混合物を濃縮した後に酢酸エチルに溶解し、水洗後、$MgSO_4$で乾燥した。溶媒を留去し、粗生成物をフラッシュクロマトグラフィーで精製して標記化合物(497 mg, 77 %)を得た。

^{1}H-NMR($CDCl_3$) δ 1.42-1.62 (m, 32H), 1.79-1.89 (m, 2H), 2.47-2.50 (m, 1H), 2.93-3.00 (m, 2H), 3.33-3.43 (m, 4H), 4.01-4.04 (m, 1H), 4.25-4.29 (m, 1H), 4.43-4.60 (m, 1H), 4.98-5.02 (m, 1H), 5.47-5.50 (m, 1H), 7.15-7.29 (m, 6H), 7.71-7.75 (m, 1H), 8.33-8.36 (m, 1H).

【0041】(b) D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド

オキザリルクロライド(79 ml, 0.91 mmol)を塩化メチレン8 mlに溶解し、-40℃でジメチルスルホキシド(129 ml, 0.91 mmol)を加え、5分間撹拌した。　上記化合物(480 mg, 0.61 mmol)を含む塩化メチレン溶液5 mlを加え、-40～-30℃で30分間撹拌した。　次いでトリエチルアミン(581 ml, 4.1 mmol)を加え、同温度で30分間撹拌した後に氷水にあけた。　有機層を分液し、水洗後、$MgSO_4$で乾燥して濃縮した。　生成物をフラッシュクロマトグラフィーで精製してt-ブトキシカルボニル-D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-4-[N', N"-ビス(t-ブトキシカルボニル)アミノイミノメチル]アミノブチル]-L-プロリンアミド(407 mg, 85 %)を得た。この化合物をアニソール1 mlに溶解し、氷冷下トリフルオロ酢酸4 mlを加え、同温度で30分間、室温で30分間撹拌した。　反応混合物を濃縮し、水5 mlに溶解し、エーテルで洗浄した後に凍結乾燥を行い標記化合物(407 mg)を得た。^{1}H-NMR(D_2O) δ 1.59-1.60 (m, 1H), 1.70-1.91 (m, 5 H), 2.12-2.14 (m, 2 H), 2.75-2.81 (m, 1 H), 3.15-3.29 (m, 4 H), 3.50-3.54 (m, 1 H), 4.43-4.46(m, 1 H), 4.53-4.61 (m, 1 H), 5.49-5.55 (m, 1 H), 7.32-7.46 (m, 5 H), 8.11-8.15 (m, 2 H); MS (SIMS) m/z 486 (M^{+1}).

【0042】(c)中間体の合成

この実施例で用いた2-[2-アミノ-5-[N',N"-ビス(t-ブトキシカルボニル)アミノイミノメチル]アミノ-1-ヒドロキシペンチル]チアゾールは以下の方法で合成した。L-アルギニン(10 g, 57 mmol)を水60mlに溶解し、4N-NaOHでpH9～10に保ちながら氷冷下クロルギ酸アリル(8.99 mg, 74 mmol)を加え、pH7に調整して同温度で2時間撹拌した。析出する沈澱物を濾取し、小量の氷水とアセトンで洗浄し、乾燥してN-アリルオキシカルボニル-L-アルギニン(13.3 g, 90 %)を得た。上記化合物(10 g, 39 mmol)とp-トルエンスルホン酸(7 g, 37 mmol)をメタノール250 mlに溶解し、ジフェニルジアゾメタン(15 g, 78 mmol)を1時間かけて加え、室温で3時間撹拌した後に濃縮した。　反応生成物をクロロホルムに溶解し、水洗後、$MgSO_4$で乾燥して濃縮し、N-アリルオキシカルボニル-L-アルギニンジフェニルメチルエステルp-トルエンスルホン酸塩(24 g)を得た。上記粗生成物(24 g)をアセトニトリル250 mlに溶解し、ジメチルアミノピリジン(4.7 g, 39 mmol)、ビス-t-ブチルジカルボネート(21 g, 97 mmol)を加え、室温で15時間撹拌した後に濃縮した。　反応混合物を酢酸エチルに溶解し、水洗後、$MgSO_4$で乾燥して濃縮し、シリカゲルクロマトグラフィー(n-ヘキサン／酢酸エチル)で精製しNα-アリルオキシカルボニル-N',N"-ビス(t-ブトキシカルボニル)-L-アルギニンジフェニルメチルエステル(14.5 g, 60 %)を得た。

【0043】上記化合物(11 g, 18 mmol)をテトラヒドロフラン150mlに溶解し、$LiBH_4$(0.75g, 35 mmol)を加え室温で2時間撹拌する。　反応混合物をpH3の酸性水にあけ、酢酸エチルで抽出し、有機層を水洗後、$MgSO_4$で乾燥して濃縮した。　反応生成物をシリカゲルクロマトグラフィー(n-ヘキサン／酢酸エチル)で精製しNα-アリルオキシカルボニル-N',N"-ビス(t-ブトキシカルボニル)-L-アルギニノール(3.9 g, 50 %)を得た。

^{1}H-NMR($CDCl_3$) δ 1.35-1.80 (m, 22H), 3.30-3.80 (m, 6H), 4.58 (d, J= 5.02Hz, 1H), 5.22 (dd, J= 1.55, 10.0 Hz, 1H), 5.31 (dd, J= 1.55, 17.6 Hz, 1H), 5.49 (d, J= 7.53 Hz, 1H), 5.93 (ddd, J= 5.02, 10.0, 17.6 Hz, 1H), 8.38 (t, J= 5.02 Hz, 1H).オキザリルクロライド(1.27 g, 10 mmol)を塩化メチレン40 mlに溶解し、-30℃でジメチルスルホキシド(1.57 g, 20 mmol)を加え5分後に上記カルビノール化合物(3.0 g, 6.7 mmol)を含む塩化メチレン溶液 20 mlを加え-30℃で30分間撹拌した。　次いでトリエチルアミン(4.62 g, 45 mmo

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l)を加えて-30℃で30分間撹拌した後、氷水にあけて分液する。 有機層を水洗後、$MgSO_4$で乾燥して濃縮し、Nα-アリルオキシカルボニル-N',N"-ビス(t-ブトキシカルボニル)-L-アルギニナール(2.9 g)を得た。

【００４４】上記粗生成物(2.9 g)と2-トリメチルシリルチアゾール(1.54 mg, 9.8 mmol)を塩化メチレン50 mlに溶解し、室温で５時間撹拌する。 1M テトラ-n-ブチルアンモニウムフルオライドTHF溶液(10.4 ml)加え、さらに３０分間撹拌し、氷水にあける。 有機層を分液し$MgSO_4$で乾燥して濃縮した。 シリカゲルクロマトグラフィー (n-ヘキサン／酢酸エチル) で精製し2-[2-アリルオキシカルボニルアミノ-5-[N',N"-ビス(t-ブトキシカルボニル)アミノイミノメチル]アミノ-1-ヒドロキシペンチル]チアゾール(2.1 g, 60 %) を得た。

^{1}H-NMR($CDCl_3$) δ 1.35-1.86 (m, 22H), 3.30-3.55 (m, 2H), 4.05-4.22 (m, 1H), 4.43-4.65 (m, 2H), 5.06-5.40 (m, 4H), 5.78-6.02 (m, 2H), 7.28 (d, J=3.0 Hz, 1H), 7.73 (d, J= 3.0 Hz, 1H), 8.48 (t, J= 6.24 Hz, 1H).

【００４５】上記化合物(2.1 g)を塩化メチレン35 mlに溶解し、ピペリジン(1.34 g, 19 mmol), $Pd(Ph_3P)_4$ (220 mg, 0.19 mmol)を加え、室温で３０分間撹拌する。反応混合物を濃縮し、シリカゲルクロマトグラフィー (クロロホルム／メタノール) で精製し標記化合物(1.42 g. 85%)を得た。

^{1}H-NMR($CDCl_3$) δ 1.40-1.80 (m, 22H), 3.17-3.55 (m, 4.70-4.80 (m, 1H), 4.88-4.98 (m, 1H), 7.40-7.80 (m, 3H), 8.30-8.43 (m, 1H).

【００４６】実施例２

2-[2-(フェニルチオアセチル)シクロペンタ-1-イルカルボニル]-L-アルギニル]チアゾール

(a) 2-[2-[2-(フェニルチオアセチル)シクロペンタ-1-イルカルボニル]アミノ-5-[N',N"-ビス(t-ブトキシカルボニル)アミノイミノメチル]アミノ-1-ヒドロキシペンチル]チアゾール

2-(フェニルチオアセチル)シクロペンタンカルボン酸(249 mg, 0.94 mmol)、2-[2-アミノ-5-[N', N"-ビス(t-ブトキシカルボニル) アミノイミノメチル]アミノ-1-ヒドロキシペンチル]チアゾール(417 mg, 0.94 mmol)、N-ヒドロキシベンゾトリアゾール(126 mg, 0.94 mmol)をアセトニトリル20 mlに溶解し、氷冷下1-エチル-3-(3'-ジメチルアミノプロピル)カルボジイミド塩酸塩(215 mg, 0.98 mmol)を加え、同温度で３時間、室温まで昇温して１５時間撹拌した。 反応混合物を濃縮した後に酢酸エチルに溶解し、水洗後、$MgSO_4$で乾燥した。溶媒を留去し、粗生成物をフラッシュクロマトグラフィーで精製して標記化合物(438 mg, 68 %)を得た。

^{1}H-NMR($CDCl_3$) δ 1.20-2.10 (m, 28H), 2.87 (m, 1H), 3.30-3.50 (m, 3H), 3.24 (m, 1H), 4.25 (m, 1H), 5.03 (m, 1H), 6.75 (m, 1H), 7.15-7.40 (m, 5H), 7.43-

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7.57 (m, 1H), 7.70 (m, 1H), 8.37 (m, 1H).

【００４７】 (b) 2-[2-(フェニルチオアセチル)シクロペンタ-1-イルカルボニル-L-アルギニル]チアゾールオキザリルクロライド(81 ml, 0.93 mmol)を塩化メチレン10 mlに溶解し、-40℃でジメチルスルホキシド(132 ml, 1.87 mmol)を加え、５分間撹拌した。 上記化合物(430 mg, 0.62 mmol)を含む塩化メチレン溶液5 mlを加え、-40～-30℃で３０分間撹拌した。 次いでトリエチルアミン(596 ml, 4.2 mmol)を加え、同温度で３０分間撹拌した後に氷水にあけた。 有機層を分液し、水洗後、$MgSO_4$で乾燥して濃縮した。 生成物をフラッシュクロマトグラフィーで精製して2-[2-(フェニルチオアセチル)シクロペンタ-1-イルカルボニル-N', N"-ビス(t-ブトキシカルボニル)アルギニル]チアゾール(350 mg, 83 %)を得た。この化合物をアニソール1 mlに溶解し、氷冷下トリフルオロ酢酸4 mlを加え、同温度で３０分間、室温で３０分間撹拌した。 反応混合物を濃縮し、フラッシュクロマトグラフィー (クロロホルム／メタノール) で精製し標記化合物(254 mg)を得た。

^{1}H-NMR(CD_3OD) δ 1.60-2.20 (m, 10H), 3.05 (m, 1H), 3.24 (m, 2H), 3.53 (m, 1H), 3.90 (m, 2H), 5.56 (m, 1H), 7.10-7.40 (m, 5H), 8.05 (m, 1H), 8.12(m, 1H); MS(FD) m/z 488 (M^+).

【００４８】(c)中間体の合成

この実施例で用いた2-フェニルチオメチルカルボニルシクロペンタン-１-カルボン酸は以下の方法で合成した。

2-[(ジフェニル)メトキシカルボニル]シクロヘキサン-１-カルボン酸(2.0 g,6.17 mmol)、トリエチルアミン(0.944 ml, 6.79 mmol)を塩化メチレン20 mlに溶解し、氷冷下、N,N-ジメチルホルムアミド(1滴)、オキザリルクロライド(855 mg, 6.79 mmol)を加え、１時間撹拌した。 次いで氷冷下、過剰のジアゾメタンを含むエーテル溶液を加え３０分間撹拌し、4N-HClジオキサン溶液 (2.31 ml) 加え更に３０分間撹拌した。 反応混合物を濃縮し、生成したクロルメチルケトンをテトラヒドロフラン30 mlに溶解し、ジイソプロピルエチルアミン(815 mg, 6.32 mmol)、チオフェノール(690 mg, 6.32 mmol)を加え、室温で３時間撹拌した後に濃縮した。 反応生成物をシリカゲルクロマトグラフィー (トルエン／酢酸エチル) で精製してフェニルチオメチルケトン(2.12 g, 86 %)を得た。この生成物をメタノール200 mlに溶解し、1M 炭酸カリウム水溶液(9.74 ml)を加えて室温で１５時間撹拌した。 反応混合物を濃縮し、残留物を水に溶解し、エーテルで洗浄した。 水層を酸性とした後に酢酸エチルで抽出し、$MgSO_4$で乾燥し、濃縮して標記化合物(0.97 g, 76 %)を得た。

^{1}H-NMR($CDCl_3$) δ 1.60-2.10 (m, 6H), 3.20 (m, 1H), 3.58 (m, 1H), 3.80 (s,2H), 7.15-7.40 (m, 5H).

【００４９】実施例３

D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]

-5-アミノペンチル]-L-プロリンアミド

(a) t-ブトキシカルボニル-D-フェニルアラニル-N-[1-[(2-チアゾリル)ヒドロキシメチル]-5-(ベンジルオキシカルボニルアミノ)ペンチル]-L-プロリンアミドt-ブトキシカルボニル-D-フェニルアラニル-L-プロリン(255 mg, 0.70 mmol)、2-[2-アミノ-6-(ベンジルオキシカルボニル)アミノ-1-ヒドロキシヘキシル]チアゾール(245 mg, 0.70 mmol)、N-ヒドロキシベンゾトリアゾール(94 mg, 0.70mmol)をアセトニトリル15 mlに溶解し、氷冷下1-エチル-3-(3'-ジメチルアミノプロピル)カルボジイミド塩酸塩(160 mg, 0.84 mmol)を加え、同温度で３時間、室温まで昇温して１５時間撹拌した。 反応混合物を濃縮した後に酢酸エチルに溶解し、水洗後、$MgSO_4$で乾燥した。 溶媒を留去し、粗生成物をフラッシュクロマトグラフィー（酢酸エチル）で精製して標記化合物(393 mg, 81 %)を得た。

^{1}H-NMR($CDCl_3$) δ 1.20-2.15 (m, 20H), 2.40-2.80 (m, 1H), 2.90-3.47 (m, 3H), 3.65-3.77 (m, 1H), 4.23-4.58 (m, 3H), 4.95-5.04 (m, 2H), 5.04-5.30 (m, 2H), 5.30-5.56 (m, 2H), 7.04-7.90 (m, 12H).

【００５０】(b) D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-5-アミノペンチル] -L- プロリンアミド

オキザリルクロライド(72 ml, 0.84 mmol)を塩化メチレン8 mlに溶解し、-40℃でジメチルスルホキシド(119 ml, 1.68 mmol)を加え、５分間撹拌した。 上記化合物(390 mg, 0.56 mmol)を含む塩化メチレン溶液5 mlを加え、-40～-30℃で３０分間撹拌した。 次いでトリエチルアミン(394 ml, 2.81 mmol)を加え、同温度で３０分間撹拌した後に氷水にあけた。有機層を分液し、水洗後、MgSO4で乾燥して濃縮した。 生成物をフラッシュクロマトグラフィー（ヘキサン／酢酸エチル）で精製してt-ブトキシカルボニル-D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-5-(ベンジルオキシカルボニル)アミノペンチル]-L-プロリンアミド(388 mg, 73 %)を得た。この化合物を蟻酸(3.5 ml)に溶解し、Pd(150 mg)を加え室温で３時間撹拌した。 反応混合物を濾過した後に濾液を濃縮し、生成物をアニソール1 mlに溶解し、氷冷下トリフルオロ酢酸(3 ml)を加え、同温度で３０分間撹拌した。 反応混合物を濃縮し、水5 mlに溶解し、エーテルで洗浄した後に凍結乾燥を行い標記化合物(190 mg)を得た。

^{1}H-NMR(D_2O) δ 1.25-2.04 (m, 7H), 2.04-2.18 (m, 1H), 2.64-2.82 (m, 2H), 3.00-3.70 (m, 6H), 4.30-4.45 (m, 2H), 5.45-5.55 (dd, J= 4.14, 9.31 Hz, 1H), 7.20-7.55 (m, 5H), 7.70-8.20 (m, 2H); MS(FD) m/z 458 (M^+).

【００５１】(c)中間体の合成

この実施例で用いた2-[2-アミノ-6-(ベンジルオキシカルボニル)アミノ-1-ヒドロキシヘキシル]チアゾールはN

α-アリルオキシカルボニル-Nω-ベンジルオキシカルボニル-L-リジンメチルエステルを出発物質として用い実施例１cと同様な方法で合成した。

^{1}H-NMR($CDCl_3$) δ 1.20-1.80 (m, 6H), 1.80-1.95 (m, 1H), 3.10-3.34 (m, 3H), 3.60-3.80 (m, 1H), 4.70 (d, J= 3.78 Hz, 1H), 4.80-4.97 (m, 1H), 5.01 (s, 2H), 7.29 (d, J= 2.52 Hz, 1H), 7.30-7.38 (m, 5H), 7.73 (d, J= 2.52 Hz, 1H).

【００５２】実施例４

D-シクロヘキシルアラニル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド

t-ブトキシカルボニル-D-シクロヘキシルアラニル-L-プロリンと実施例１cの化合物から実施例１と同様な方法で合成した。

^{1}H-NMR(D_2O) δ 1.00-1.55 (m, 4H), 1.55-2.25 (m, 14H), 2.30-2.40 (m, 1H),3.22-3.30 (m, 2H), 3.58-3.70 (m, 1H), 3.72-3.82 (m, 1H), 4.39 (dd, J= 3.45, 13.8 Hz,1H), 4.56 (dd, J= 8.6 Hz, 1H), 4.80-5.80 (m, 1H), 8.10-8.23(m, 2H); MS(SIMS) m/z 492 (M^{+1}).

【００５３】実施例５

D-フェニルグリシル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド

t-ブトキシカルボニル-D-フェニルグリシル-L-プロリンと実施例１cの化合物から実施例１と同様な方法で合成した。

^{1}H-NMR(D_2O) δ 1.62-1.97 (m, 8H), 2.10-2.20 (m, 1H), 2.98-3.06 (m, 1H), 3.22-3.30 (m, 1H), 3.63-3.72 (m, 1H), 4.58 (dd, J= 3.40, 8.60 Hz, 1H), 5.38-5.43 (m, 1H), 5.50-5.60 (m, 1H), 7.45-7.60 (m, 5H), 8.10 (d, 1H), 8.20 (d, 1H); MS(SIMS) m/z 472 (M^{+1}).

【００５４】実施例６

D-チロシル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド

t-ブトキシカルボニル-D-チロシル-L-プロリンと実施例１cの化合物から実施例１と同様な方法で合成した。

^{1}H-NMR(D_2O) δ 1.75-2.04 (m, 6H), 2.16-2.36 (m, 2H), 3.04-3.10 (m, 1H), 3.25-3.28 (m, 3H), 3.45-3.46 (m, 1H), 3.70-3.76 (m, 1H), 4.52-4.77 (m, 2H), 5.52-5.56 (m, 1H), 6.85-6.96 (m, 2H), 7.19-7.26 (m, 2H), 8.13-8.19 (m, 2H); MS(SIMS) m/z 504 (M^{+2}).

【００５５】実施例７

D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-オクタヒドロインドール-2-カルボキシアミド

t-ブトキシカルボニル-D-フェニルアラニル-L-オクタヒドロインドール-2-カルボン酸と実施例１cの化合物から実施例１と同様な方法で合成した。

^{1}H-NMR(D_2O) δ 0.87-1.05 (m, 2H), 1.10-1.23 (m, 3

H), 1.36-1.49 (m, 3H), 1.58-1.82 (m, 5H), 1.91-2.03 (m, 2H), 2.85-3.00 (m, 2H), 3.15-3.20 (m, 3H), 4.20-4.25 (m, 1H), 4.34 (dd, J= 5.4, 10.3 Hz, 1H), 5.38 (dd, J= 4.0,8.4 Hz, 1H), 7.19-7.36 (m, 5H), 7.98-8.04 (m, 2H); MS (SIMS) m/z 540 (M^{+1}).

【００５６】実施例８

ベンジルオキシカルボニル-D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド

ベンジルオキシカルボニル-D-フェニルアラニル-L-プロリンと実施例１cの化合物から実施例１と同様な方法で合成した。

^{1}H-NMR($CDCl_3$) δ 1.40-2.20 (m, 7H), 2.59-2.80 (m, 1H), 2.90-3.50 (m, 5H), 3.50-3.80 (m, 1H), 4.28-4.54 (m, 1H), 4.54-4.70 (m, 1H), 5.04 (ABq, J=13.8, 39.7 Hz, 1H), 5.45-5.70 (m, 1H), 6.18-6.30 (m, 1H), 6.90-7.50 (m,10H), 7.65 (d, J= 7.36 Hz, 1H), 7.84 (d, J= 7.36 Hz, 1H), 7.94-8.04 (m,1H); MS(SIMS) m/z 620 (M^{+1}).

【００５７】実施例９

アセチル-D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド

アセチル-D-フェニルアラニル-L-プロリンと実施例１cの化合物から実施例１と同様な方法で合成した。

^{1}H-NMR(D_2O) δ 1.50-2.50 (m, 11H), 2.52-2.75 (m, 2H), 2.97-3.13 (m, 2H),3.15-3.50 (m, 2H), 3.65-3.80 (m, 1H), 4.35-4.50 (m, 1H), 5.35-5.50 (m, 1H), 7.23-7.56 (m, 5H), 8.00-8.22 (m, 2H); MS(SIMS) m/z 528 (M^{+1}).

【００５８】実施例１０

3-フェニルプロピオニル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド

3-フェニルプロピオニル-L-プロリンと実施例１cの化合物から実施例１と同様な方法で合成した。

^{1}H-NMR(D_2O) δ 1.50-2.50 (m, 6H), 2.50-3.25 (m, 8H), 3.25-3.57 (m, 2H), 4.28-4.38 (m, 1H), 5.40-5.46 (m, 1H), 7.20-7.40 (m, 5H), 7.60-7.70 (m, 1H), 8.00-8.10 (m, 1H); MS(SIMS) m/z 471 (M^{+1}).

【００５９】実施例１１

4-フェニルブタノイル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド

4-フェニルブタノイル-L-プロリンと実施例１cの化合物から実施例１と同様な方法で合成した。

^{1}H-NMR($CDCl_3$) δ 1.72-1.75 (m, 2H), 1.89-2.09 (m, 5H), 2.26-2.51 (m, 5H), 2.61-2.68 (m, 2H), 3.13-3.56 (m, 4H), 4.42-4.53 (m, 1H), 5.59 (brs, 1H), 7.08-7.28 (m, 5H), 7.70 (d, J= 3.1 Hz, 1H), 7.77-7.90 (m, 2H), 8.00(d, J= 3.1 Hz, 1H); MS (SIMS) m/z= 485 (M^{+1}).

【００６０】実施例１２

D-プロリル-N-[1-[(2-チアゾリル)カルボニル]-4-グアニジノブチル]-L-プロリンアミド

t-ブトキシカルボニル-D-プロリル-L-プロリンと実施例１cの化合物から実施例１と同様な方法で合成した。

^{1}H-NMR(D_2O) δ 1.70-2.20 (m, 9H), 2.30-2.45 (m, 1H), 2.47-2.65 (m, 2H), 3.25-3.35 (m, 1H), 3.40-3.55 (m, 2H), 3.60-3.68 (m, 1H), 3.70-3.80 (m,1H), 3.80-3.90 (m, 1H), 4.58 (dd, J= 3.40, 5.17 Hz, 1H), 4.68 (dd, J= 6.90,7.59 Hz, 1H), 5.51 (dd, J= 5.17, 9.31 Hz, 1H), 8.12 (d, J= 3.40 Hz, 1H), 8.18 (d, J= 3.40 Hz, 1H); MS(FD) m/z 435 (M^+).

【００６１】実施例１３

2-[2-(フェニルチオアセチル)シクロヘキサ-1-イルカルボニル-L-アルギニル]チアゾール

2-(フェニルチオアセチル)シクロヘキサンカルボン酸と実施例１cの化合物から実施例２と同様な方法で合成した。

^{1}H-NMR(CD_3OD) δ 1.10-2.20 (m, 12H), 2.63 (m, 1H), 3.02 (m, 1H), 3.09-3.23 (m, 2H), 3.83-4.09 (m, 2H), 5.47-5.55 (m, 1H), 7.05-7.40 (m, 5H), 8.02 (m, 1H), 8.10 (m, 1H); MS(SIMS) m/z 502 (M^{+1}).

【００６２】実施例１４

4-フェニルブタノイル-N-[1-[(2-チアゾリル)カルボニル]-5-アミノペンチル]-L-プロリンアミド

4-フェニルブタノイル-L-プロリンと実施例３cの化合物から実施例３と同様な方法で合成した。

^{1}H-NMR(D_2O) δ 1.40-2.25 (m, 10H), 2.35 (m, 2H), 2.65 (m, 2H), 2.99 (m, 2H), 3.42-3.52 (m, 4H), 4.40 (m, 1H), 5.46 (m, 1H), 7.10-7.40 (m, 5H), 8.05 (m, 1H), 8.11 (m, 1H); MS(SIMS) m/z 457 (M^{+1}).

【００６３】実施例１５

3-フェニルプロピオニル-N-[1-[(2-チアゾリル)カルボニル]-5-アミノペンチル]-L-プロリンアミド

3-フェニルプロピオニル-L-プロリンと実施例３cの化合物から実施例３と同様な方法で合成した。

^{1}H-NMR(D_2O) δ 1.20-1.90 (m, 7H), 1.90-2.20 (m, 2H), 2.50-3.00 (m, 5H), 3.20-3.54 (m, 2H), 4.29-4.37 (m, 1H), 5.39 (dd, J= 3.75, 8.00 Hz, 1H), 7.12-7.35 (m, 5H), 7.98 (d, J= 2.77 Hz, 1H), 8.06 (d, J = 2.77 Hz, 1H); MS(SIMS) m/z 443 (M^{+1}).

【００６４】実施例１６

D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-6-アミノヘキシル]-L-プロリンアミド

t-ブトキシカルボニル-D-フェニルアラニル-L-プロリンと2-[2-アミノ-7-(ベンジルオキシカルボニル)アミノ-1-ヒドロキシヘプチル]チアゾールから実施例３と同様な方法で合成した。

^{1}H-NMR(D_2O) δ 1.20-1.90 (m, 9H), 2.00-2.20 (m, 2H), 2.74 (ddd, J= 6.90,7.24, 7.59 Hz, 1H), 2.98-3.10 (m, 2H), 3.10-3.32 (m, 2H), 3.39-3.50 (m,1H),

4.44 (dd, J= 4.83, 9.66 Hz, 1H), 4.50-4.60 (m, 1H), 5.48 (dd, J= 4.14, 9.66 Hz, 1H), 7.25-7.50 (m, 5H), 8.10 (d, J= 2.41 Hz, 1H), 8.15 (d, J= 2.41 Hz, 1H); MS(SIMS) m/z 471 (M^{+1}).

【0065】実施例17

3-フェニルプロピオニル-N-[1-[(2-チアゾリル)カルボニル]-6-アミノヘキシル]-L-プロリンアミド

3-フェニルプロピオニル-L-プロリンと2-[2-アミノ-7-(ベンジルオキシカルボニル)アミノ-1-ヒドロキシヘプチル]チアゾールから実施例3と同様な方法で合成した。

^{1}H-NMR(D_2O) δ 1.20-1.90 (m, 10H), 1.90-2.08 (m, 1H), 2.08-2.30 (m, 1H), 2.54-2.85 (m, 1H), 2.85-3.06 (m, 6H), 3.25-3.35 (m, 1H), 3.40-3.61 (m, 2H), 4.41 (d, J= 6.90 Hz, 1H), 5.43 (dd, J= 3.45, 8.60 Hz, 1H), 7.14-7.37(m, 5H), 8.02 (d, J= 24 Hz, 1H), 8.08 (d, J= 24 Hz, 1H); MS(FD) m/z 456(M^+).

【0066】実施例18

D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-4-メトキシブチル]-L-プロリンアミド

t-ブトキシカルボニル-D-フェニルアラニル-L-プロリンと2-(2-アミノ-1-ヒドロキシ-5-メトキシペンチル)チアゾールから実施例1と同様な方法で合成した。

^{1}H-NMR($CDCl_3$) δ 1.57-1.59 (m, 1H), 1.73-1.88 (m, 5H), 2.07-2.14 (m, 2H), 2.75-2.78 (m, 1H), 3.20-3.33 (m, 2H), 3.35 (s, 3H), 3.49-3.56 (m, 3H), 4.42 (dd, J= 4.2, 8.5 Hz, 1H), 4.53 (m, 1H), 5.49 (dd, J= 4.3, 8.4 Hz, 1H), 7.31-7.34 (m, 2H), 7.41-7.46 (m, 3H), 8.09 (d, J= 3.1 Hz, 1H), 8.14(d, J= 3.1 Hz, 1H); MS (FD) m/z 459 (M^{+1})

【0067】実施例19

D-フェニルアラニル-N-[1-[(2-ベンゾチアゾリル)カルボニル]-4-メトキシブチル]-L-プロリンアミド

t-ブトキシカルボニル-D-フェニルアラニル-L-プロリンと2-(2-アミノ-1-ヒドロキシ-5-メトキシペンチル)ベンゾチアゾールから実施例1と同様な方法で合成した。

^{1}H-NMR($CDCl_3$) δ 1.74-1.78 (m, 1H), 1.80-1.93 (m, 4H), 2.04-2.19 (m, 2H), 2.73-2.74 (m, 1H), 3.15-3.28 (m, 2H), 3.35 (s, 3H), 3.54-3.58 (m, 4H), 4.40-4.45 (m, 1H), 4.50-4.54 (m, 1H), 5.56 (dd, J= 4.3, 8.4 Hz, 1H), 7.24-7.43 (m, 5H), 7.67-7.73 (m, 2H), 8.15-8.26 (m, 2H); MS (SIMS) m/z= 509 (M^{+1}).

【0068】実施例20

t-ブトキシカルボニル-D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-4-メトキシブチル]-L-プロリンアミド

t-ブトキシカルボニル-D-フェニルアラニル-L-プロリンと2-(2-アミノ-1-ヒドロキシ-5-メトキシペンチル)チアゾールから合成される実施例18の中間体として得た。

^{1}H-NMR(D_2O) δ 1.51-1.90 (m, 14H), 2.15-2.23 (m, 2H), 2.62-2.66 (m, 1H), 3.01-3.04 (m, 2H), 3.30 (s, 3H), 3.38-3.44 (m, 3H), 3.54-3.57 (m, 1H), 4.49-4.62 (m, 2H), 5.40-5.43 (m, 1H), 5.75-5.79 (m, 1H), 7.18-7.32 (m, 5H), 7.53-7.61 (m, 2H), 7.95-7.98 (m, 1H), 8.18-8.21 (m, 1H); MS(FD) m/z 558 (M^+).

【0069】実施例21

t-ブトキシカルボニル-D-フェニルアラニル-N-[1-[(2-ベンゾチアゾリル)カルボニル]-4-メトキシブチル]-L-プロリンアミド

t-ブトキシカルボニル-D-フェニルアラニル-L-プロリンと2-(2-アミノ-1-ヒドロキシ-5-メトキシペンチル)ベンゾチアゾールから合成される実施例19の中間体として得た。

^{1}H-NMR(D_2O) δ 1.43 (s, 9H), 1.51-1.67 (m, 4H), 1.80-1.89 (m, 2H), 2.07-2.21 (m, 2H), 2.61-2.63 (m, 1H), 2.90-3.05 (m, 2H), 3.30 (s, 3H), 3.33-3.40 (m, 2H), 3.51-3.54 (m, 1H), 4.44-4.48 (m, 1H), 4.62-4.64 (m, 1H), 5.44-5.47 (m, 1H), 5.55-5.62 (m, 1H), 7.20-7.31 (m, 5H), 7.63-7.65 (m,1H),7.68 (d, J= 3.0 Hz, 1H), 8.02 (d, J= 3.0 Hz, 1H); MS(FD) m/z 608 (M^+).

【0070】実施例22

D-フェニルアラニル-N-[1-[(2-チアゾリル)カルボニル]-2-フェニルエチル]-L-プロリンアミド

t-ブトキシカルボニル-D-フェニルアラニル-L-プロリンと2-(2-アミノ-1-ヒドロキシ-3-フェニルプロピル)チアゾールから実施例1と同様な方法で合成した。

^{1}H-NMR($CDCl_3$) δ 1.49-1.54 (m, 2H), 1.60-1.80 (m, 1H), 2.10-2.14 (m, 1H), 2.59-2.67 (m, 1H), 2.85-2.97 (m, 2H), 3.10-3.19 (m, 1H), 3.28-3.49 (m,2H), 3.64-3.75 (m, 1H), 4.50-4.54 (m, 1H), 5.88-5.93 (m, 1H), 7.20-7.36(m, 10H), 7.67-7.78 (m, 2H), 8.06-8.08 (m, 1H); MS (SIMS) m/z 477 (M^{+1}).

【0071】実施例23

4-フェニルブタノイル-N-[1-[(2-チアゾリル)カルボニル]エチル]-L-プロリンアミド

4-フェニルブタノイル-L-プロリンと2-(2-アミノ-1-ヒドロキシプロピル)チアゾールから実施例1と同様な方法で合成した。

^{1}H-NMR(D_2O) δ 1.52 (d, J= 6.90 Hz, 1H), 1.80-2.30 (m, 6H), 2.30-2.38 (m,2H), 2.68-2.74 (m, 2H), 3.30-3.40 (m, 1H), 3.45-3.52 (m, 1H), 4.62 (dd, J= 2.41, 9.31 Hz, 1H), 5.69 (q, J= 6.90 Hz, 1H), 7.18-7.31 (m, 5H), 7.69 (d, J= 3.10 Hz, 1H), 8.02 (d, J= 3.10 Hz, 1H); MS(FD) m/z 399 (M^+).

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